MONOGRAPHS ON NEOPLASTIC DISEASE AT VARIOUS SITES

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NEOPLASTIC DISEASE
AT VARIOUS SITES

General Editor
D. W. SMITHERS, M D., F.R.C P., F.F.R.

VOLUME I

CARCINOMA OF THE LUNG

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GENERAL INTRODUCTION TO THE SERIES OF MONOGRAPHS ON NEOPLASTIC DISEASE AT VARIOUS SITES

THIS book is one of a series of monographs on neoplasms at individual sites. The intention is to present a detailed clinical picture of the range of neoplastic disease taking place in one particular organ or tissue at a time. The general scheme is to discuss for each site what is known of the factors leading to the development of neoplasia and the possibilities of prevention or postponement which arise from them; to consider the pathology and natural history of the disease as a means to understanding its course and modes of spread, and thus to have a more secure basis both for planning treatment and for judging its results, to examine the methods of diagnosis of the earliest manifestations or of the pre-neoplastic changes occurring, in the hope of learning to deal with these tumours more frequently and more effectively before they have ceased to be a local problem, and to assess the methods of treatment now available and their value alone or in combination so as to review what is being achieved and to see what more could reasonably be expected. A good deal of variation in presentation has been allowed for, however, because of the very different problems which arise from site to site and which themselves made this method of detailed particularization in the clinical discussion of neoplastic disease seem so desirable at the present time.

Much has been written about cancer without clear definition of what is being discussed. Many of the causative factors would seem to be organ- or tissue-specific, or at least local in their action. The natural history of this group of diseases differs markedly from one site of origin to another, even, in some special cases, when separated by no more than a few millimetres The diagnostic problems often relate more to other diseases involving the sites in question than to cancer as an ill-defined disease entity. The really effective treatments that are available are still local ones in the great majority of cases and even those which do have some beneficial effect upon the disseminated disease are mostly specific to site of origin. A good deal more could now be done with present methods of treatment for patients with neoplastic disease if the best that is available was more generally applied, and further progress still would result at many sites from earlier treatment.

Vague generalizations about cancer are at present of little use to the individual patients suffering from the disease; a specific particularization about neoplasms at a given site is often of immediate practical value and may point the way to a deeper understanding The detailed clinical approach to this great problem may be in danger of occupying rather less of our attention than it deserves because of a wishful expectation that some simple solution covering all sites of origin will one day be provided for us

One of the chief difficulties in the study of neoplastic disease at individual sites is in obtaining sufficient clinical experience. Although these diseases are common, so many parts are involved and the patients are so widely distributed throughout the medical service, that few doctors see many patients with tumours of one particular tissue or organ during their whole lifetime. In 1944 a group of postgraduate teaching hospitals in London started a scheme for joint consultation and co-operation in the treatment of patients with certain tumours In this way they hoped to pool their experience and to acquire sufficient clinical material for detailed study. This series of monographs is based on the work of this group of hospitals and has been made possible by the large number of patients with tumours at individual sites seen by members of the staffs concerned. It is not intended that the material for these books should be strictly confined to this hospital group, however, but that they should include wide clinical experience wherever it may be found and enlist expert help whenever it is available.

Both the co-operating hospital scheme and the preparation of this series of monographs have for long been of great personal interest to me and I am extremely grateful to my colleagues in my own and in the other hospitals concerned for their unselfish and generous assistance. I took my plan to Mr Charles Macmillan of Messrs E & S. Livingstone Limited in 1955 and was met with enthusiasm and an immediate promise of help which has been [illegible] since that day. His response has now led to the establish- [illegible] work on the part [illegible]

Each resulting monograph, in its final form, appears through the efforts of an individual editor working within the general framework laid down. I owe a personal debt of gratitude to each one of them for their forbearance, enthusiasm and unstinted labour. I am also deeply indebted, as they are, to the many contributors who have worked with us in our attempt to realize our aim.

D. W. SMITHERS

LONDON, 1958

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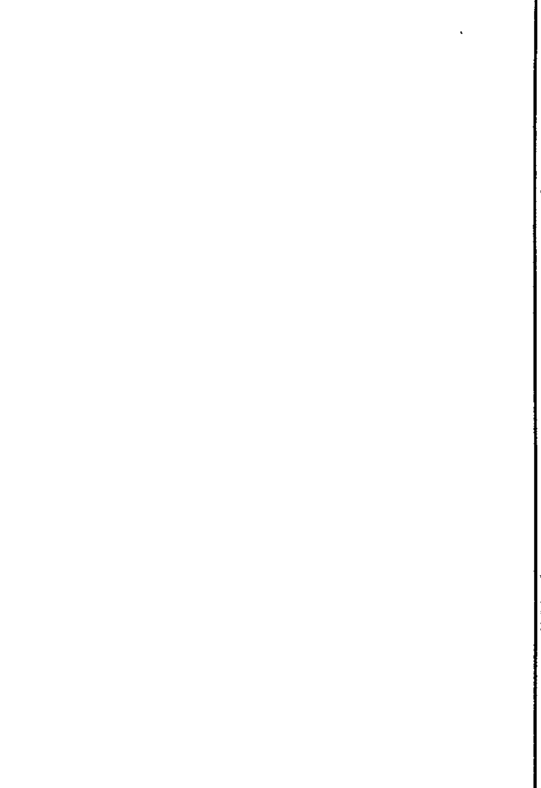
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J. R. Bignall

London, 1958



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CONTENTS

INTRODUCTION

HISTORICAL NOTES

Is it worth while to write a monograph on the subject of primary malignant tumours of the lung? In the course of the last two centuries an ever-increasing literature has accumulated around this subject . . .

> *Adler, I.* (1912): *Primary Malignant Growths of the Lungs and Bronchi, p.* 3. *Longmans, Green, London.*

Je passe sous silence l'etiologie et le traitement de cette maladie, qui, jusqu'a présent, est hors du domaine de l'art.

> *Heyfelder, M.* (1837): *Du Cancer des Poumons. Arch. gen. Med.* (*3rd series*), **2,** 345.

INTRODUCTION

Historical Notes

J. R. Bignall

ALMOST all the common clinical manifestations of intrathoracic cancer were clearly and accurately described during the nineteenth century. It is difficult to differentiate the intrathoracic tumours reported into the modern pathological classes; but the account of a case given by Bayle in 1810 has been described as the earliest full record of a patient with a primary lung cancer. It has been referred to many times, the English translation of 1815 is worth quoting

37th Observation

Union of the Cancerous and Tubercular Phthisis in a person remarkably affected with cancerous diathesis.

A labourer, 62 years of age, of a sanguine temperament, was admitted to the Charité the 30th June 1805. He had considered himself ill only during the last six weeks. His disorder began with general pains, which obliged him to quit his work. His chest and epigastrium in particular, were in a state of extreme sufferance, and he had a slight cough accompanied with a white and opake expectoration. For ten days he had eat nothing, and twice he had vomited spontaneously. From that moment the constipation became habitual, and there were sharp transient pains at the fundament; the faecal matter resembled goats' dung . . . The liver formed an unequal and large tumour which occupied the epigastrium, and extended even to the naval. . . . There were three hard, indolent, movable oblong bodies, smaller

and had always a frequent pulse, red face and pretty sharp pains in the abdomen, which did not increase on pressure. There was often vomiting of liquid matter, yellowish and bilious. The tongue became dry, then brown, and lastly black; but for the last days it was almost clean. the cough was become frequent, the expectoration purulent and pretty copious. the strength diminished daily. In spite of the emaciation and extreme feebleness, the face remained tolerably red till he expired, the 18th of July, at two in the morning . .

Opening of the Body

Thorax—The lungs scarcely adhered to the contiguous parts, appeared pretty sound, but were a little obstructed. In cutting them, one found at the root of the lung, *in an extent of nearly four inches long by two broad, a shining white substance, in* the interior of which were some capillary blood vessels. In compressing this substance, which resembled a little the appearance of brain, thick white matter issued from it, a good deal like cream. There were some portions of tubercular

matter placed here and there in this white substance, and the surrounding pulmonary tissue. The tubercular degeneracy, which was of a whitish and opake yellow, contrasted in a remarkable manner with the cancerous matter, which was of a shining white. There were small tubercles and very small purulent foci in all the lobes, so that on pressing the lungs, but particularly the left, a little purulent matter was forced out . . .

Abdomen—The liver was very large and quite filled with white bodies sunk into its substance, as large as nuts, walnuts, or even Indian chesnuts, all shining, and of a milk-white colour. . . . There was found a white schirrus body as large as a nut, fixed upon the pancreas. . . The mobile and ovoid bodies placed upon the sides of the chest, were small brain-like cancerous affections . . .

REMARKS—*In this man there was a general cancerous affection, and a tubercular degeneracy united to cancer in the organ of respiration . . .*

and Brown.

* * *

In 1838 Dr E. S. Hare, house-surgeon to the Stafford County General Infirmary, published a case report of a 'Tumor Involving Certain Nerves' in the *London Medical Gazette* This describes most of the clinical pattern now called the Pancoast syndrome, although the primary may not have been a lung cancer.

Thomas Willetts, aged 40, married, of an unhealthy complexion, was admitted to the Infirmary, under the care of Dr Knight, on the 8th of last June He had been attacked a month before with pain, tingling and numbness along the course of the ulnar nerve of the left arm, which was most severe at the elbow, where there had also been some swelling and redness. There was, besides, pain through the *left shoulder, extending across the chest to the opposite side, and upwards to the* left eye and teeth of that side, also a sense of pulsation in different parts of the body, and sleepless nights. The tongue was clean, appetite good, no cough, or ... and the secretions were all natural

the left side of the neck, which it ...
on the origins of the nerves going ...
wrist was equal to that of the oth... ...
to be more than an enlarged gland, and the disease was supposed to be of a scrofulous nature.

In addition to the foregoing symptoms, the pupil of the left eye became contracted; and the levator palpebrae ceased to perform its office, the general irritability increased almost to mania, and the bowels became very torpid. In about three weeks after his admission, the pains and distressing sensations appeared to be increased, the pulse had become quicker, there were signs of debility, with numbness and coldness of the lower extremities; also by this time the tumor of the neck had become more extensive, and possessed a remarkable degree of hardness.

On the 20th of July he had almost entirely lost the power of sensation and

motion in the lower extremities; and in a day or two afterwards there was complete retention of urine . . . his strength gradually failed till the 26th of August, when trismus came on with paralysis of the muscles of deglutition and expectoration; and he died from suffocation at four o'clock on the following morning . . .
Post-mortem inspection— . . the tumor was seen to extend upwards as far as the origin of the brachial plexus The carotid artery, internal jugular vein, and pneumo-gastric nerve, passed into its substance, the first remaining pervious, the two last lost and transformed into the diseased structure, as were also the phrenic nerve, and further down the sympathetic, with its lowest cervical ganglion The jugular vein above the tumor was atrophied, and the pneumo-gastric was oedematous. The scirrhous mass extending under the clavicle, the latter was removed, and the following were its further relations —The subclavian artery and vein passed into its substance, that portion of the anterior scalenus which separates the artery and the vein, and nearly the whole of the muscle, being included in the disease, and undistinguishable. Both the artery and the vein were pervious, but the latter was filled with a coagulum of a deep red colour. The tumor extended inwards as far as the trachea and arteria innominata, and downwards behind the left vena innominata and subclavian and carotid arteries, as far as the aorta, impinging upon it at the junction of its arch with the descending portion The thoracic duct passed into and was lost in the disease, as also were the recurrent laryngeal nerve, and the veins accompanying the branches of the subclavian artery,—the branches of that artery themselves passed through the tumour without being converted into its nature The tumor lay upon the brachial plexus, being firmly attached to the spine at the origin of the third and fourth nerves of the plexus, both which were inseparable from it. the carcinomatous mass extended itself in company with the last cervical and first dorsal nerves between the transverse processes, and into the intervertebral foramina as far as to the dura mater, which appeared beginning to be implicated, but the canal was perfect, and the appearance of the theca of the medulla not at all altered. There was no appearance of carcinoma in any other part of the body.

Hare, E. S (1838): '*Tumor Involving Certain Nerves*'. *Lond. med Gaz.*, **1**, 16

* * *

In *A Treatise on the Diagnosis and Treatment of Diseases of the Chest*, published in 1837, William Stokes gave a good description of superior vena caval obstruction. The book was reprinted by the New Sydenham Society in 1882.

A man, aged thirty-six, about a year previous to his final admission into the Meath Hospital, was attacked with occasional stitches of the right side, followed by cough, hoarseness, dyspnoea, and scanty mucous expectoration—after some time a little tinged with blood. The face and neck became oedematous, and the swelling was observed to be greater on the right side . . .

. . . He experienced some difficulty of swallowing, and referred the obstruction to the lower part of the throat, . . . *The right jugular vein was much distended, as were the veins in the right axilla, but this symptom was chiefly remarkable on the surface of the belly, where two veins corresponding to the situation of the superior epigastric artery pursued a remarkably tortuous course along each side of the linea alba, being turgid and dilated to the size of swan quills.* . .

> Another remarkable phenomenon developed itself before the termination of the disease; whenever he lay down, that instant a loud wheezing was heard in his chest, accompanied by a sensation of imminent suffocation; . . . (p. 386).

* * *

John Cockle wrote a monograph, *On Intra-thoracic Cancer*, published in 1865. Of the pain of cancer he said:

> Although pain of most variable seat, character, and degree of intensity, is of very frequent occurrence during some period of the course of thoracic cancer, it certainly cannot be regarded either as invariable or characteristic. . . . When present, it may occupy some circumscribed region, or extend far and wide . . . It may be dull, deep, and fixed, unchanged in amount by pressure; or superficial, remittent, intermittent, lancinating, radiating, conjoining with excessive sensibility of the surface, and much increased by cough or movement (pp. 70–71)

He described laryngeal paralysis as a complication:

> The voice . . may be rendered hoarse, and nearly extinct, by congestion and superficial ulceration, or cracked, or the extinction of voice may exist without any sign of obstruction in the larynx, and without either stridor or dyspnoea, being dependent solely on paralysis of the laryngeal muscles consequent on pressure upon the nerves by the cancerous mass within the chest (pp. 73–74).

Of treatment he wrote:

> The difficulties of diagnosis once surmounted, how little can be said respecting either the prognosis or treatment of a disease which, being inevitably fatal, restricts all interference of art to measures of simple palliation (p. 103).

And of the manner of dying:

> Although it is beyond our power to predicate the mode of death in any given case of intrathoracic cancer, the following may be enumerated among the more common and immediate. Asphyxia, chronic or acute, induced either by acute miliary deposit throughout the tissue of the lung, or from the pressure of tumours in the posterior mediastinum upon the main bronchi, or from encroachment on the lungs by anterior mediastinal tumour, or from pulmonary congestion and oedema, sudden and extensive serous or sero-sanguineous effusion into the pleural or pericardial sacs, coagulation of blood in the pulmonary artery (Walshe), general disorganisation of the parenchyma of the lung, inducing extensive suppuration and gangrene. In protracted cases, death is, also, at times, the direct result of asthenia and exhaustion, or it may occur during slight convulsion. Lastly, death may be immediately caused by haemoptysis, or actual suffocation has occurred from sudden escape of pus from an excavation in the lower lobe of the left lung . . . (pp. 69–70) During the closing stage, when the anguish is, at times, of fearful intensity, morphia, in frequent doses, is indispensable, with the direct intention of favouring the *euthanasia* (p 104).

* * *

James Risdon Bennett gave the Lumleian Lectures of the Royal College of Physicians in 1870 on the subject of *Cancerous and other Intra-thoracic Growths, their Natural History and Diagnosis*, published in 1872 Bennett was

one of the first physicians of the City of London Hospital for Diseases of the Chest (now the London Chest Hospital), being appointed in 1849. Among the case reports of primary lung cancers are the following:

> Case 6. *Cancer of bronchial glands, right apex, etc.*—Eliz. Spall, aged 49, a married woman . . . of spare habit of body, looking much older than the age she gave herself, . . . stated that for five or six months she had suffered from cough and shortness of breath, attended with loss of appetite and of flesh, and considerable debility . . .
>
> Ten days after admission, there was a considerable amount of dyspnoea, or sense of breathlessness, even when quiet, . . . Paroxysms of extreme orthopnoea and distress then became frequent, compelling her to retain the upright posture; and distinct laryngeal stridor attended the breathing. . . . Stimulants and opiates gave a certain amount of relief; but she sank, apparently from exhaustion occasioned by the extreme dyspnoea and incessant paroxysm of cough . . (pp. 65–67)
>
> Case 11. *Intra-thoracic cancer, involving the bronchial glands, spinal column, etc.* . . . A. K., aged 23, single, a servant girl, was admitted into the Victoria Park Hospital, under the care of Dr Risdon Bennett, on the 29th of October 1867. She was a well-grown girl, rather spare, with brown hair and eyes, . whilst away for her holiday at Whitsuntide, she had felt very unwell and out of sorts. . . After a month's absence, she returned to town, feeling much better, and went to service. In about a fortnight, however, she broke down, the catamenia became suppressed; she had haemoptysis to the extent of three or four ounces, with some cough and expectoration; the latter, however, was but scanty . .
>
> On the 15th November, she complained, for the first time of pain between the shoulders, . . . she . . gradually lost power in the lower extremities, . . .
>
> On the 3rd January, there was observed, for the first time, a projection of the third lumbar vertebra. . . . On the 5th, for the first time, there was much dyspnoea, with mucous rhonchi and dusky countenance . . . she did not finally sink till the 12th of January, when she died apparently from asthenia (pp. 122–127).

* * *

Concerning the rarity of lung cancer, Adler, in his monograph on *Primary Malignant Growths of the Lungs and Bronchi*, published in 1912, wrote.

> . . . there is nearly complete consensus of opinion, and that is that primary malignant neoplasms of the lungs are among the rarest forms of disease. Within the last few decades attempts have been made to combat this dogma . . (p. 3). There seems hardly room for doubt that the increase in the percentage of lung tumours is to be attributed mainly to the increased attention paid to these types of tumour and the greater care and more extensive microscopic investigation with which autopsies are carried out at present (pp 10–11). . . . It is the conviction of the writer, and he shares his belief with many others—the mention of whose names and criticism of whose work need not be entered upon here—that there is no absolute increase in the incidence of carcinoma. Nevertheless, the incidence of malignant neoplasms of the lungs seems to show a decided increase. It has been stated that statistical research in this direction is beset with many difficulties (p. 7).

SECTION ONE

THE MORTALITY FROM CANCER OF THE LUNGS IN ENGLAND AND WALES

of the population, broken down by age and sex, for the whole of England and Wales; with broader age groupings for the standard regions, conurbations, and aggregates of urban and rural areas outside the conurbations The smaller geographical subdivisions are merely provided with an estimate of the total population distinguished by sex but without any age breakdown.

Death Registration

By law, all deaths must be notified to the local registrar of births and deaths within a short time of their occurrence. The age, sex, address and cause of death of the deceased are entered on the certificate, thus allowing death to be classified by sex, age and geographical location For males and single females the last occupation is also recorded, but for married females the husband's occupation only is stated. For this reason the occupational records relating to females are almost useless.

The cause of death entered on the certificate is affected by various imponderable influences. The diagnostic skill of the medical practitioner, current fashions in diagnosis, a desire not to offend the patient's relatives, and the hospital facilities of the district may influence the entry. In some cases the causes of death may be multiple, and a priority must be attached to one for classification purposes.

The classification of disease is in itself a major problem. and the classifications used have had to be changed from time to time. The one at present in use is the International Statistical Classification of Diseases, Injuries, and Causes of Death, Sixth Revision 1948 (World Health Organization 1948).

Each year the Registrar General publishes his Annual Statistical Review of England and Wales. This contains a return of all deaths, distinguished by sex and by, at present, 718 disease classes in five-year age groups; less detailed tables for the major geographical subdivisions; and a statement of the number of deaths, distinguished by sex but not by age, for the minor geographical subdivisions.

Indices

A series of indices can be derived from the population and number of deaths in each year by simple arithmetical methods, and it is wise to spend some time considering the nature of the statement made by each, so that the appropriate one may be used in answering any particular question. This is not really such a simple matter as it sounds, and medical writings abound in confusion caused by neglecting this elementary precaution The indices that we may meet in this book are discussed in Appendix I (p. 270).

Some of these indices, notably the crude death rate and the group of age-standardized summarizing indices that includes the age-standardized death rate, the standardized mortality ratio (S M.R.) and the comparative mortality index (C.M.I.) are extremely misleading when one is considering the biological nature of a disease. (The reason for this is discussed in Appendix I (p. 274))

Because of this I have avoided the use of summarizing indices as far as possible. In subsequent chapters, where other authors have perforce to use such indices, it is wise to consider what aspect of the raw data they emphasize.

Cohort Analysis

Since the age-specific disease-specific death rates can be calculated for England and Wales in fairly small age groups (five-year) from information published yearly, the variation of the intensity of the attack of killing diseases at different ages can be mapped fairly accurately. The rates for cancer of the lungs are shown in Tables I and II. Each vertical column of rates, distinguished by a date, is called a 'contemporary array of age-specific death rates'. Contemporary is used in the sense of referring to the *same date*, not in the sense of referring to the *present time*

TABLE I

Contemporary Arrays of Age-specific Death Rates for Cancer of the Lungs. England and Wales 1911–55. Males.

The data are arranged in a form suitable for cohort analysis.
(*From Case and Pearson* 1956.)

Age (*years*)	1911–15	1916–20	1921–25	1926–30	1931–35	1936–40	1941–45	1946–50	1951–55
0–	0·000	0·000	0·001	0·001	0·001	0·001	0·001	0·000	0·001
5–	*0·000	*0·000	*0·000	*0·000	*0·000	*0·000	*0·000	*0·000	0·000
10–	*0·001	*0·001	*0·001	*0·001	*0·000	*0·001	*0·001	*0·001	0·000
15–	*0·002	*0·002	*0·002	*0·002	*0·002	*0·002	*0·002	*0·003	0·002
20–	*0·003	*0·003	*0·003	*0·004	*0·005	*0·006	*0·006	*0·008	0·007
25–	*0·005	*0·004	*0·005	*0·007	*0·010	*0·014	*0·016	*0·018	0·013
30–	*0·007	*0·006	*0·008	*0·011	*0·020	*0·030	*0·034	*0·036	0·035
35–	0·011	0·011	0·018	0·022	0·054	0·068	0·081	0·094	0·098
40–	0·017	0·015	0·027	0·052	0·087	0·149	0·191	0·236	0·248
45–	0·030	0·025	0·044	0·076	0·186	0·274	0·384	0·544	0·579
50–	0·046	0·040	0·066	0·112	0·256	0·431	0·597	0·954	1·224
55–	0·062	0·055	0·087	0·148	0·348	0·586	0·883	1·350	2·003
60–	0·070	0·076	0·101	0·181	0·364	0·646	1·021	1·717	2·555
65–	0·076	0·086	0·113	0·169	0·354	0·636	0·970	1·763	2·926
70–	0·069	0·071	0·097	0·158	0·349	0·533	0·748	1·400	2·624
75–	0·052	0·052	0·086	0·133	0·276	0·464	0·631	1·095	2·069
80–	0·021	0·041	0·050	0·094	0·189	0·324	0·385	0·765	1·416
85+	0·035	0·008	0·031	0·029	0·167	0·176	0·248	0·471	0·901
80+	0·025	0·032	0·045	0·078	0·183	0·286	0·346	0·682	1·274
All ages	0·015	0·015	0·024	0·042	0·095	0·164	0·245	0·400	0·611

Age-specific death rates per thousand living per year.
Based on figures including non-civilians
* = interpolated rates.

TABLE II

Contemporary Arrays of Age-specific Death Rates for Cancer of the Lungs. England and Wales. 1911–55. **Females.**

The data are arranged in a form suitable for cohort analysis.
(*From Case and Pearson* 1956.)

Age (years)	1911–15	1916–20	1921–25	1926–30	1931–35	1936–40	1941–45	1946–50	1951–55
0–	0 000	0 000	0 000	0 000	0 001	0 000	0 001	0 000	0 000
5–	*0 000	*0 000	*0 000	*0 000	*0 000	*0 000	*0 000	*0 000	0 000
10–	*0 001	*0 001	*0 000	*0 001	*0 001	*0 001	*0 001	*0 001	0 000
15–	*0 001	*0 001	*0 001	*0 001	*0 001	*0 001	*0 001	*0 001	0 000
20–	*0 001	*0 001	*0 001	*0 001	*0 002	*0 003	*0 002	*0 003	0 003
25–	*0 002	*0 002	*0 002	*0 002	*0 004	*0 005	*0 006	*0 006	0 005
30–	*0 003	*0 003	*0 003	*0 003	*0 007	*0 008	*0 011	*0 012	0 015
35–	0 008	0 005	0 004	0 009	0 013	0 016	0 022	0 024	0 027
40–	0 011	0 010	0 012	0 016	0 025	*0 032*	*0 036*	0 048	0 051
45–	0 020	0 014	0 021	0 023	0 041	0 049	0 057	0 073	0 087
50–	0 027	0 022	0 026	0 032	0 055	0 078	0 093	0 117	0 137
55–	0 031	0 034	0 034	0 058	0 078	0 107	0 124	0 169	0 203
60–	0 039	0 036	0 050	0 061	0 118	0 153	0 170	0 221	0 281
65–	0 046	0 034	0 050	0 069	0 132	0 179	0 201	0 302	0 349
70–	*0 054*	*0 038*	*0 050*	*0 074*	*0 117*	*0 192*	*0 226*	*0 316*	*0 383*
75–	0 040	0 029	0 039	0 073	0 121	0 184	0 205	0 309	0 425
80–	0 017	0 031	0 029	0 049	0 095	0 152	0 172	0 280	0 391
85+	0 023	0 008	0 063	0 040	0 066	0 090	0 143	0 196	0 307
80+	0 019	0 024	0 039	0 046	0 086	0 133	0 163	0 252	0 363
All ages	0 009	0 008	0 011	0 016	0 030	0 044	0 054	0 077	0 099

Age-specific death rates per thousand living per year.
Based on figures including non-civilians.
* = interpolated rates.

If the groupings of ages and of dates are chosen in such a way that each age-specific death rate is a mean value for an age-date group that has equal sides (*i.e.*, 1 × 1 year, 5 × 5 years, 10 × 10 years), then a series of rates is formed that enables us to follow the threat of death from various causes that has hung [illegible] and thus to differen-

[illegible]

important posthumous paper in 1939, though used earlier by Cherry (1925) amongst others, can give a useful picture of how a contemporary array of age-specific death rates for a population in a particular calendar year is built up Although we have not sufficient data relating to the past to use cohort analysis for making detailed international comparisons of mortality, the contemporary arrays of age-specific mortality data shown in Tables IV and V can more readily be comprehended if we make use of the insight into their origin that cohort analysis can give.

For this reason the fundamental principles of cohort analysis as a background to the understanding of contemporary arrays of age-specific death rates are discussed in Appendix I (pp. 272–274).

The foregoing remarks are general in character, and can refer to mortality rates for any disease. When we come to consider cancer of the lungs we know that environmental influences are important in producing the disease, and we know that in the environmentally induced form of the disease there is a long latent period between the beginning of the application of the stimulus and the occurrence of the disease. The average latent period may be between fifteen and twenty years (see Chapter V, p. 58). These circumstances make it of special importance that we consider the contemporary age-specific death rates in the light of the historical approach of cohort analysis, because changes of environment that took place many years ago may only now be exerting their effect.

CHAPTER II

MORTALITY FROM CANCER OF THE LUNGS IN ENGLAND AND WALES

R. A. M CASE

MORTALITY IN ENGLAND AND WALES AS A WHOLE

Numbers of Deaths from Cancer of the Lungs in England and Wales

DURING the last calendar year for which the final figures have been published (1956) 15,615 males and 2,571 females were certified as dying of cancer of the lungs. In these cases the disease was either certified as being of primary origin (11,409 males and 1,878 females) or it was not stated whether the disease was primary or secondary (4,206 males and 693 females). The figures take no account of cases where a pulmonary neoplasm was certified as being of secondary origin (Registrar General, 1957.)

Cohort Analysis of Death Rates from Cancer of the Lungs in England and Wales

The age-specific death rates for cancer of the lungs in England and Wales since 1911 are shown in Tables I and II (Chapter I, pp. 13-14). The data are arranged in five-year age groups and five-year date groups (Case and Pearson, 1956) These Tables provide sufficient data to enable us to use the method of cohort analysis mentioned and described in Appendix I (pp 272–274) to show how the present age-specific death rate pattern has evolved.

Figure 1 shows the situation in a simplified form. Four cohorts, formed by quinary-quinquennial grouping as described by Case (1956*a*), are used for the analysis. The people in these cohorts were born around the central years 1871, 1881, 1891 and 1901 and they are chosen because:—(1) The 1871 cohort attained the 80–84 age group in 1951–55 and thus became statistically extinct, passing into the indeterminate age group called 85 and over, for which no meaningful death rate can be computed (2) A period of ten years between each cohort is convenient because it does not obscure the picture with too much detail, as the consistent use of a five-year interval would do. (3) The age group 50–54 is about the lowest at which analysis of the trend is profitable, and this is the age group attained by the 1901 cohort in the last quinquennium for which we have data (1951–55). (The cohort lines in the picture drawn in this [illegible] the lines joining the tops of each series of chequered panels [illegible] ntemporary age-specific death rates at [illegible] ndix I (p. 273).)

We can now see that for both males and females the death rate for cancer of the lungs is initially very low but rises throughout the life span.

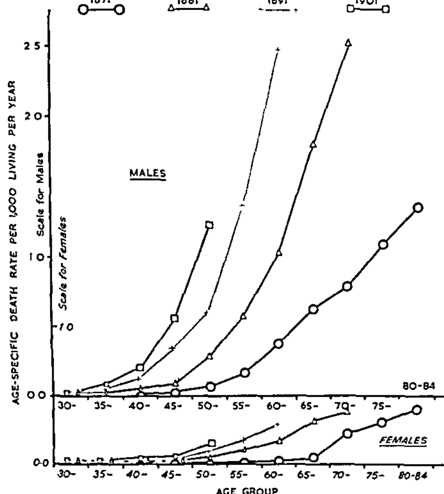


Fig 1

Cohort analysis of age-specific death rates for cancer of the lungs, England and Wales, 1911–55. Males and females shown separately. (After Case 1956*b*)

Interpretation of the Death Rates

The Age-effect in Cohort Data—The change of the death rate with the advancing age of the members of the cohorts (as in Figure 1) is due to a variety of causes. It may in part be due to an effect inseparable from the individual's age as such (nature), and it may in part be due to environmental factors to which the individual has been subjected during his lifetime (nurture). The environmental

of any age group are by definition not the same set of individuals, nor th survivors of the same set of individuals as the members of any other age group. *The age-specific death rates of any two age groups in the* contemporary arra cannot therefore be construed as referring to one individual's chances of dyin in a stated time, but each must refer to a different individual's chance of dying. Furthermore, the different individuals must have lived through a partiall different set of years and as a consequence may have been exposed to differen environmental factors.

The apparent 'cancer age' effect shown by Figure 2 is in fact only on *instance of a phenomenon that will always occur when the secular* change an the age-effect reach a certain critical relationship. The nature of this relationshi is discussed in Appendix I on page 281.

Sex Difference in Cohort Death Rates for Cancer of the Lungs in England and Wales

of secular change for the females lags behind the male trend by some 20 years. The *magnitude of the female rates is much less than that of the males.* The sex difference shown is much higher than that found for other sites of cancer that are common to both sexes (Case 1956*b*). (Breast cancer might be regarded as an exception to this, but the male breast is vestigial and comparison at this site is unjustified.)

Whilst it is a common finding that males suffer a higher mortality than females from most diseases from which they both may suffer, this does not necessarily imply that such a difference is an inherent one. In most societies the sexes occupy different positions in the social structure, so that one sex may be subjected to influences which may be different in magnitude in, or wholly absent from, the environment of the other.

Factors that might Affect Recorded Death Rates from Cancer of the Lungs in England and Wales

In considering the mortality *data it must always be borne in mind that* the rates shown are based on *recorded* death rates. As such they will be influenced by many changing factors, amongst which are environment, accuracy of diagnosis, efficiency of treatment and changing social habits. Theoretically at least, a varying genetical pattern of the population must be considered as a source of change, though methods of measuring this have not yet been devised ... the influence of all these ... ement ... death rate from cancer of the lungs in this and other countries must, however, be discussed because of the long and largely profitless controversy that has been raging.

The Influence of Improved Diagnosis on the Recorded Death Rates

There has been an undoubted improvement in precision of diagnosis of cancer of the lungs during the last half-century, and there can be few who would claim that the effect of this improvement can be measured with accuracy. There are, however, some instances where calculations meant only to explore possible limits of error have inadvertently lent a spurious air of mathematical respectability to wild surmise

Some recent authors (*e.g.*, Gilliam 1956; Registrar General 1957) have considered what groups of diseases might contain the cases of lung cancer that were misdiagnosed and have concluded that the general classification 'Other Respiratory Diseases' has been the usual residuary legatee The diseases included in this category are respiratory tuberculosis, bronchiectasis, lung abscess, pulmonary fibrosis, pleurisy with effusion, chronic bronchitis, bronchopneumonia and pneumonia. They propose that a certain *proportion* of this class 'Other Respiratory Diseases', at a date around 1911–20, should be con- [illegible]

[illegible]

conclusion (p. 136):—

> 'In this age-group in 1911–20 the average annual death rate among men from the main group of respiratory diseases other than cancer of the lung was 6,511 per million If the death rate from lung cancer had been the same in this decade as it was in 1955 the number of wrongly certified deaths would have been 2,475 per million, and if all these had been wrongly attributed to the 'other respiratory group' it would imply mis-diagnosis in 38 per cent, a proportion that it is difficult to accept *If, however, only 10 per cent of the other respiratory group were wrongly diagnosed* and certified, the 1911–20 rate of 64 per million would become 715 per million and the lung cancer in this age-group would have increased 3 6 times instead of 40 times.' (i e between 1911–20 and 1955)

Gilliam (1956), who had used similar arguments, had suggested that a 2 per cent error in the diagnosis of 'Other Respiratory Diseases' in America would reduce the apparent increase of lung cancer mortality of males in that country, recorded as being twenty-six-fold over the period 1914 to 1950, to fourfold.

In my opinion this approach uses a kind of inverted logic. It does not seem a very reasonable procedure to calculate the number of *misdiagnosed* cases of lung cancer by measuring the number of *diagnosed* cases of a very large group of other diseases and then allotting a fixed proportion of that number to lung cancer.

The question we wish to answer is: 'What proportion of the deaths that were in fact due to lung cancer were attributed to that cause?' As we have seen, the Registrar General's (1957) statement about the 55–64 year-old group of [illegible]

[illegible]

'Other Respiratory Diseases' shows a diagnostic error of only 10 per cent in relation to the wrongful inclusion of lung cancer.

We can, however, legitimately express the same figures in another way, and say that these two rates mean that in 1911–20 only one out of about twelve true lung cancer deaths were certified as such, a diagnostic error of about 92 per cent in relation to the wrongful exclusion of lung cancer.

If for the moment we accept as plausible the statement that in 1911–20 92 per cent of true lung cancer cases at age 55–64 were not diagnosed terminally as such, and assume the error at the present time to be nearly negligible, we are left *with a rather less than fourfold (3·6 times) increase of the true age-specific* death rate from lung cancer instead of the recorded increase of fortyfold. If we now go on to consider the case of males aged 20–24, we must first decide whether we think that it was more or less easy in 1911–20 to make a correct terminal diagnosis of lung cancer than it is now, and whether the present day error at this age is negligible or is large.

We have seen that an improvement in terminal diagnosis from a 92 per cent error to a negligible error at age 55–64 would account for an apparent twelvefold rise in the rate between 1911–20 and 1955. (This figure is the difference between the rise of 3·6 times suggested by the Registrar General and the recorded rise of 40 times over the period 1911–20 to 1955.) The recorded rise at age 20–24 over the same period is only just over twofold. To accommodate this fact, we must approach one of two extremes. One is to say that the terminal diagnosis at age 20–24 in 1911–20 was of a very high standard, one case out of every two being correctly diagnosed, instead of one out of twelve as at age 55–64, and that at present the error is negligible. The other is to say that at present terminal diagnosis at age 20–24 is extremely poor, only one case out of about six being correctly diagnosed, whereas at age 55–64 the error is negligible; and that in 1911–1920 at age 20–24, as at age 55–64, only one out of about twelve cases was correctly terminally diagnosed. It is relevant to recall that in the last decade or so much attention has been paid to the examination of the chests of young adults, by radiographic and other methods, as part of the campaign against tuberculosis.

The Registrar General recognized that the methods he had applied to males aged 55–64 would produce highly implausible results if applied to females, but surmounted the difficulty by saying (p. 138):—

> 'In addition, there are numerous arguments both for and against the hypothesis that any diagnostic error should be of the same magnitude in both sexes.'

Broadly speaking, any claims that a considerable proportion of the rise in recorded death rates from lung cancer in the last fifty years is due to improved diagnosis must be based on an hypothesis or on hypotheses that can accommodate the following observations:—

(1) There are wide variations in the increase in the recorded age-specific death rates for both males and females. At age 20–24 the increase from 1911–15 to 1951–55 is between twofold and threefold for both sexes; at age 55–64 it is about thirty-four-fold for males and about sevenfold for females.

(2) There are wide variations in the sex-ratios at different ages and at

different dates. At present (1951–55) at age 20–24 the male/female ratio is 2·3 to 1; at age 55–64 it is 9·4 to 1. In 1911–15 these ratios were 3·0 to 1 and 1·9 to 1 respectively.

By 'a considerable proportion of the rise in the recorded death rate' I mean a proportion that would with propriety absolve medical men from the obligation of searching for relatively recent and widespread causes of what has elsewhere been described by Doll (1954) as a pandemic.

Whether or not a consideration of all the circumstances of the changes in the practice of clinical medicine, of the use of ancillary diagnostic techniques, and of the circumstances that lead to or prevent people of different sexes or ages seeking medical examination could plausibly explain these observations is outside the scope of this chapter.

Equally, any hypothesis, or set of hypotheses, that purports to link some genetically, therapeutically or environmentally changed situation with the recorded increase must also be able to accommodate the same observations.

Discussion of the Secular Trend of Death Rates from Lung Cancer in England and Wales

Judged by cohort analysis, the secular trend of a rising rate is a fairly rare feature of cancer mortality in England and Wales. The only other sites (amongst those defined by the Registrar General in 1913) that show a rising rate are: in both sexes, kidneys and adrenals, pancreas, leukaemia and Hodgkin's disease; in the male, urinary bladder; and in the female, ovaries and Fallopian tubes (Case 1956*b*.)

Figures 3 and 4 have been drawn to put the death rates for cancer of the lungs into perspective They show the cohort picture for all causes of death, for cancer of all sites, and indicate the contribution of cancer of the lungs and of some other groups of sites In order to make some features of the mortality pattern of the later [illegible]
altered for each coho[illegible]
the picture finishes [illegible]
cohort or cohorts at the relevant age has been included in each picture

The situation revealed by these figures may be described (Case 1956*b*) in the following way In all the cohorts the male general mortality, age for age, always exceeds the female general mortality, and the male cancer mortality exceeds the female cancer mortality at all ages above 55. The general mortality is decreasing at all ages shown for females, and at all ages under 60 for males. The male 1891 cohort has an unfavourable mortality at age 60–64 compared with the 1881 cohort, though still favourable when compared with the 1871 cohort

The cancer mortality for males increases in each successive cohort, whilst that for females decreases. The most dramatic feature of the cancer mortality when broken down into the large subdivisions is the increase in mortality from cancer of the lungs in males. In the 1871 cohort cancer of the lungs was never a major item in the balance sheet. In the 1901 cohort at the age of 50–54, cancer of the lungs accounts for about half of the total cancer mortality rate

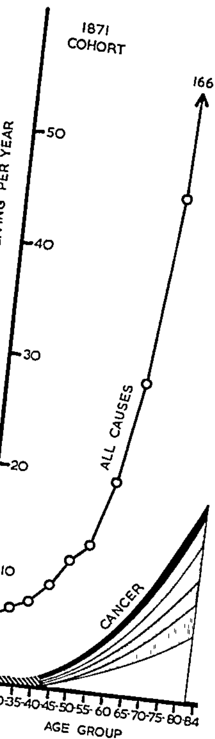


Fig 3

ge-specific death rate picture for mortality in England and Wales by cohort analysis Males. uses of death and the contributions made by cancer at all sites, cancer of the lungs and by the other main sites are shown

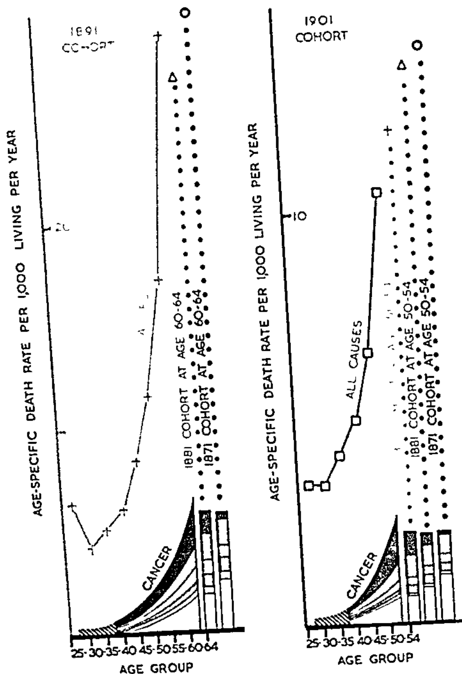
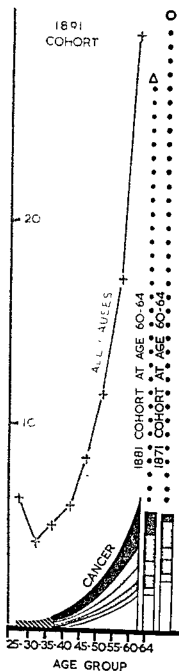


FIG 3
Continued
For key to sites of cancer, see Fig. 4 overleaf

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The age-specific death rate picture for mortality in England and Wales by cohort analysis Males All causes of death and the contributions made by cancer at all sites, cancer of the lungs and by the other main sites are shown.



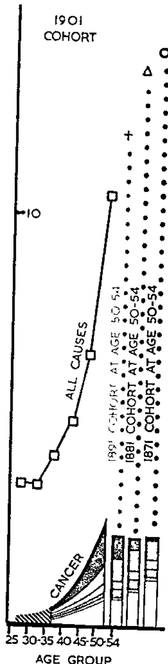
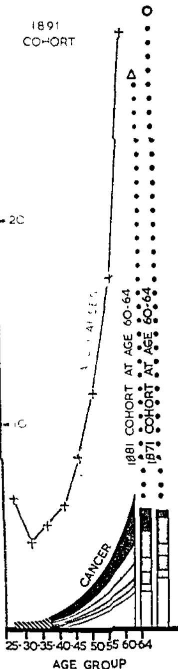


FIG 3
Continued
For key to sites of cancer, see Fig 4 overleaf.

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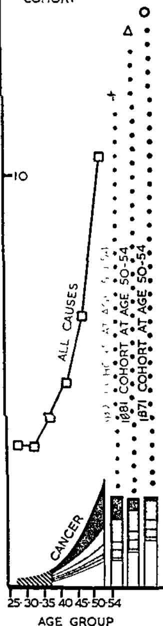


Fig 3
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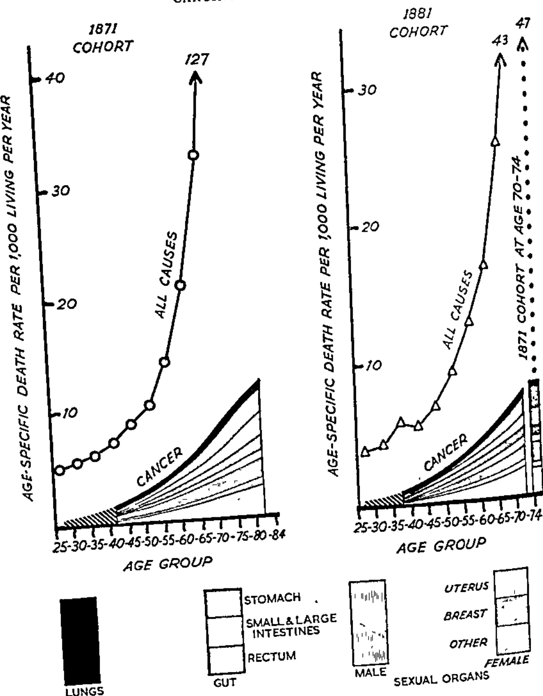


FIG 4 ... Wales by cohort analysis Females. ... and by

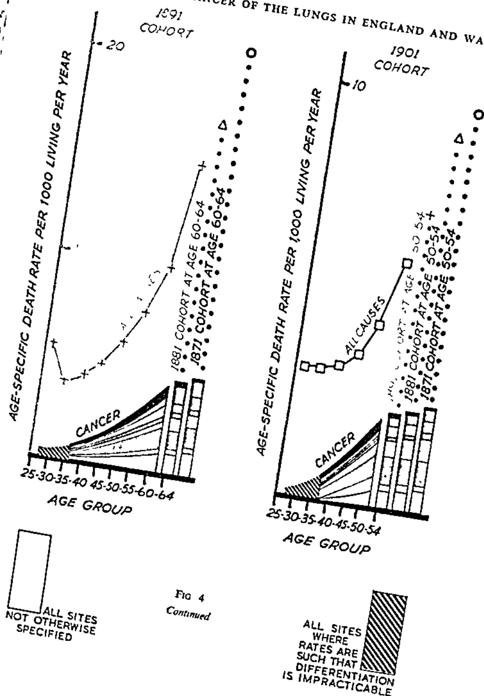


FIG 4
Continued

and for about one-eighth of the total mortality rate. In the female the rate for cancer of the lungs, though increasing, has not yet assumed major importance. The mortality rate from all forms of cancer other than cancer of the lungs shows a progressive decrease in each succeeding cohort in both sexes, but a form of presentation which uses grouped sites does not throw much light on how this comes about.

The increase in the male mortality from cancer of the lungs from the 1881 cohort to the 1891 cohort at the age of 60–64 is in itself sufficiently great to account for the increase in general mortality already discussed at that age. This is not to say that it is in fact solely responsible for this increase

Figures 5 and 6 have been drawn to emphasize how the recorded increase of male death rates from cancer of the lungs has contributed to the widespread notion that there has been a recent great increase in the death rate from cancer at all sites.

Figure 5, cancer at all sites, shows that the male cancer mortality rates for each successive cohort exceed those for the preceding cohort; at age 50–54, the most advanced age at which all four cohorts are depicted, the mortality rate of the 1901 cohort is 122 per cent of that of the 1871 cohort at the same age. The female cancer mortality rates have decreased in each successive cohort; the mortality rate of the 1901 cohort at age 50–54 is only 82 per cent of that of the 1871 cohort at that age

Figure 6 shows the mortality rates for cancer at all sites except the lung. In both males and females there is now a progressive diminution in the rate for each successive cohort, the male rate for the 1901 cohort at age 50–54 being 68 per cent of that for the 1871 cohort at that age, and the female rate for the 1901 cohort 78 per cent of that of the 1871 cohort

The justification for analysing the cancer death rates with and without the contribution due to the mortality ascribed to cancer of the lung lies in the division of contemporary thought about the recorded increase of the mortality from lung cancer. One school, as we have seen, maintains that the increase is almost entirely spurious, being the result of improved diagnosis. If this is true, since it would seem that most of the misdiagnosed cases would previously have been allocated to some disease category other than cancer, a progressively larger amount must be added to the total cancer mortality rate of each cohort as the date of birth grows more remote. The final picture will then show a progressively diminishing cancer mortality, as in the female The other school, whilst not denying that diagnostic changes have taken place, asserts that a considerable part of the increase is due to environmental influences under human control. If this view is correct, the remedy lies in removing these influences. The interest in cancer mortality will then be transferred to the residual sites of cancer, where as yet we cannot make any confident assertion about the causation of any large fraction of the mortality experience.

Variations of Mortality within England and Wales

The figures that we have considered are the national rates Within any community, however, there are factors at work which may prevent an even

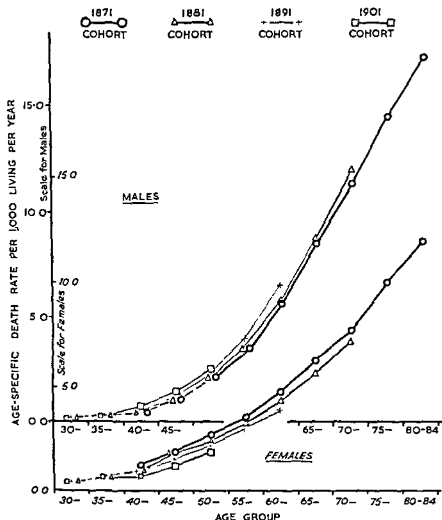


Fig 5

Cohort analysis of age-specific death rates for cancer at all sites England and Wales 1911–55 Males and females shown separately (After Case 1956*b*)

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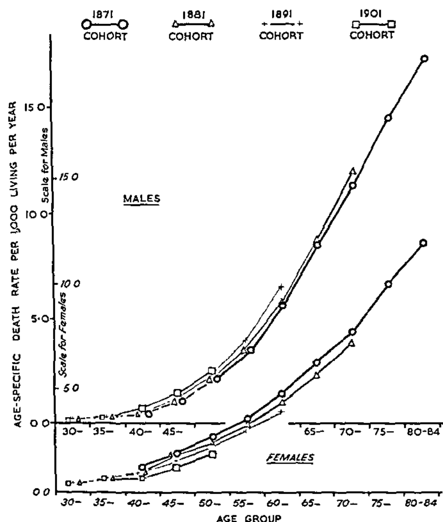


FIG 5

Cohort analysis of age-specific death rates for cancer at all sites. England and Wales 1911–55
Males and females shown separately (After Case 1956*b*)

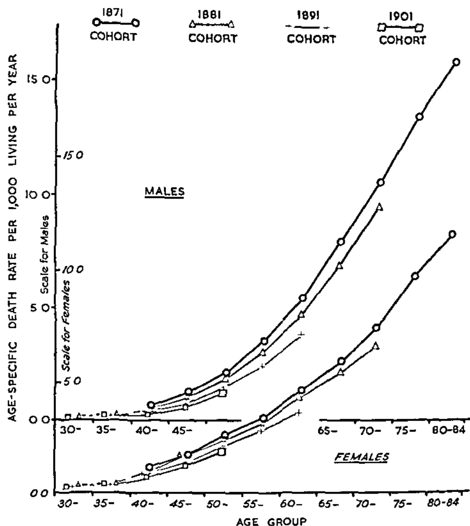


FIG 6
Cohort analysis of age-specific death rates for cancer at all sites except lungs England and Wales. 1911–55 (After Case 1956*b*)

distribution of diseases. It is usual to distinguish at least three types of variation that should be studied from this viewpoint:—

(a) Seasonal effects

(b) Economic, social and occupational effects.

(c) Geographical effects. These may be subdivided into urban-rural differentiation effects and local effects

When we come to subdivide the mortality data to study these variations our information is less detailed than the national annual returns and we are often forced to use indices which may demonstrate that variations exist but which do not help us to gain much insight into how they have evolved (see Appendix I, pp. 274–281).

Seasonal Effects

The death rates from cancer of the lungs show a cyclical seasonal change, being lower in the summer months and higher in the winter ones This almost certainly reflects the prevalence of respiratory infection as a terminal event rather than any real change in the morbidity rate of lung cancer.

This cyclical variation is shown for males in 1950–55 in Figure 7. The short period of time covered by the analysis renders the use of the crude death rate legitimate here (see Appendix I, pp. 283).

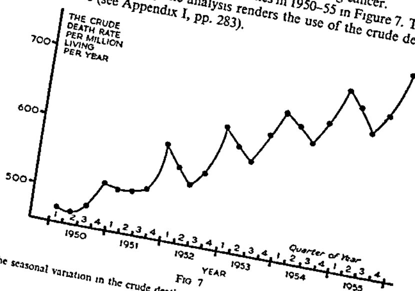


Fig 7

The seasonal variation in the crude death rate from cancer of the lungs. England and Wales. 1950–55. Males.

Economic, Social and Occupational Effects

Economic and Social Effects

The most commonly used stratification is the Social Class grouping adopted by the Registrar General. The current definition is given by him (Registrar

General 1954 p. 1) in Part I of the Decennial Supplement. The grouping is not entirely satisfactory as an index of economic effects, since it is based on the social status of occupational groups, and may in individual cases have little relevance to income.

In two studies (Registrar General 1927 p. xxiii, 1938 p. 44) of the information gathered at the Census of 1921 and that of 1931, 'the evidence for an association between cancer of the lung and social class was somewhat equivocal . . .' (Logan 1954).

A preliminary report (Registrar General 1954 p. 11–23) on the 1951 Census reveals a fairly definite trend of rising death rates from cancer of the lungs from Social Class I (richest) to Social Class V (poorest) for males aged 20–64. The standardized mortality ratios range from 80 (S.C. I) to 116 (S.C. V).

The death rates for males over 60 and for married women do not show this trend. Single women are not discussed.

Occupational Effects

These are discussed elsewhere (Chapter V).

Geographical Effects

Urban-Rural Effects

Many forms of cancer show an increased mortality in urban districts as compared with rural ones. Stocks (1937) points out that 'this is not due, as is sometimes stated, to the fact that many cancer patients resident in country districts die in town hospitals, since each death is transferred to and counted in the place of residence of the deceased except in the case of a small number who had no fixed abode. The differences between urban and rural death rates from cancer must be attributed, therefore, to other factors.' Cancer of the lung is one of the forms of cancer the death rate for which tends to be higher in urban areas than in rural ones. This phenomenon first attracted the official notice of the Registrar General (1940) around 1937, and the topic has been discussed by him in many of the later volumes of the Statistical Review. Table III is modified from the 1955 (Registrar General 1957) commentary volume and shows the variation in death rates that is currently found.

Stocks and Campbell (1955) undertook a detailed investigation into the effect of certain atmospheric pollutants, which they showed to be present in increasing quantities with increasing urbanization, on lung cancer death rates of cigarette smokers classified by tobacco consumption. They found that the rural-urban differentiation was always apparent amongst each of the various classes of cigarette smokers. This paper is discussed more fully in Chapter vii.

Local Effects

Table III shows that it is not the degree of urbanization alone that determines the magnitude of the death rate, for equally urbanized communities in different parts of the country have different rates.

TABLE III

Regional Variation in Standardized Mortality Rates for Cancer of the Lungs. 1950–54. (From Registrar General 1957 p. 149.)

	Males	*Females*
England and Wales .	100	100
NORTH OF ENGLAND	101	99
Standard regions		
Northern	87	89
East and West Ridings	98	95
North-Western	110	106
Conurbations		
Tyneside .	115	116
West Yorkshire	102	92
South-East Lancashire	120	112
Merseyside	142	133
Urban areas	107	103
Rural Districts	62	70
MIDLANDS AND EASTERN ENGLAND	89	88
Standard regions		
North Midland	79	81
Midland .	100	91
Eastern .	86	90
Conurbation		
West Midland	119	97
Urban areas	103	93
Rural Districts .	63	79
SOUTH OF ENGLAND	109	113
Standard regions		
London and South-Eastern	123	127
Southern	91	90
South-Western	78	83
Conurbation		
Greater London	127	137
Urban areas	116	117
Rural Districts	73	84
WALES (including Monmouthshire)	78	71
Wales I (South-East)	84	70
Wales II (remainder)	64	73
Urban areas	88	76
Rural Districts	59	59
URBAN AND RURAL AGGREGATES		
Urban areas .	108	105
Conurbations	125	123
Areas outside conurbations	85	86
Urban areas with populations of 100,000 and over .	111	100
Urban areas with populations of 50,000 and under 100,000	93	90
Urban areas with populations under 50,000 .	84	85
Rural Districts	66	77

St[illegible]
cally
in a [illegible] maps to show the local [illegible] rates for the years 1921–30. Figures 8 and 9 are reproductions of two of these, for cancer of the lungs in males and females respectively. He (Stocks 1936) warns readers that the local distribut[illegible] be 'greatly influenced by the lack of unifor[illegible] and under such circumstances it is [illegible] clusions as to the incidence.' One f[illegible] (1947) showed to have a high correlation with the incidence of lung cancer was the mean annual sunshine hours. In discussion of this finding he says (p. 16), 'The cause of the difference in annual sunshine is partly geography, partly climate and partly smokiness in the atmosphere.' He later elaborates this theme and continues,

Actual mortality per cent of that expected from the distribution of population by age and class of district



FIG 8

Regional variations in mortality from cancer of the lungs 1921-30 Males Age 25 and over. (From Stocks 1936)

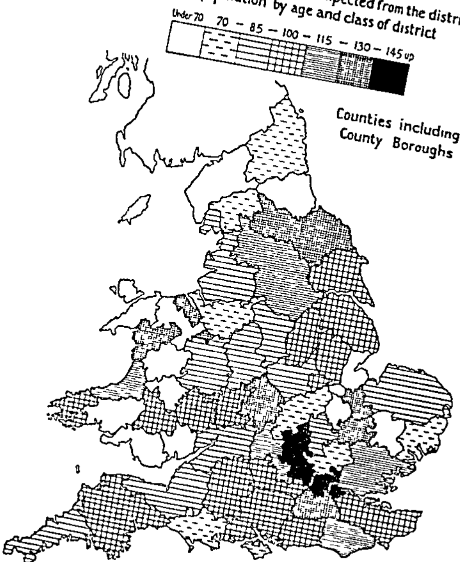


Fig 9

Regional variations in mortality from cancer of the lungs, 1921–30 Females. Age 25 and over. (From Stocks 1939)

'The only explanations of the above results (*i.e.*, the negative correlation of lung cancer mortality and sunshine) which seem adequate are that either smokiness of the atmosphere is an important factor in producing cancer of the lung, or sunshine is an important factor in preventing its incidence' (Bracketed portion inserted.)

In fact, since a variety of man-made environmental factors can influence lung cancer mortality, the local variations that have been discussed above may have been caused in part at least by the quality of local community life and practice rather than be the effects of factors inherent in the geographical situation of the areas considered.

Personal Habits

The proposition that the smoking of tobacco is part of a causal nexus in the aetiology of a considerable proportion of cancer of the lungs is examined critically elsewhere in this book (Chapter VI).

MORBIDITY SURVEYS (ENGLAND AND WALES)

So far we have limited our discussion to death rates. In the future it is hoped that a considerable increase of our knowledge of cancer will accrue from studies of morbidity and prevalence.

At present, although cancer registration schemes, either at the national or regional level, are being enthusiastically pressed, we have not achieved a sufficiently complete system of recording cases of cancer to allow morbidity rates to be calculated with anything like the precision of mortality rates. For this reason morbidity data have been excluded as a topic for discussion in the foregoing.

This does not imply that the data already collected are not extremely valuable in other types of statistical studies, such as assessment of treatment, which are outside the scope of this discussion.

CONCLUSIONS

Cohort analysis of the lung cancer mortality in England and Wales as a whole has shown that for both males and females the death rate is very low until the third and fourth decades, but thereafter it rises throughout the remainder of the life span. In addition to this change with age, there is a secular increase of rate which is much more pronounced for the males than for the females. Part of this secular change, how much cannot be determined, is due to improvements in diagnosis. It seems highly probable that after allowing for this diagnostic change there is a marked true rise in rate, more apparent amongst males than amongst females. An explanation of this true rise must probably be sought in changes of habit, environment and racial genetic characteristics that have occurred during the last half-century. Other fluctuations of death rates are found. These include seasonal variation, a social class gradient amongst males under sixty-five, an urban-rural differentiation, and a geographical variation within England and Wales.

CHAPTER III

COMPARISON OF MORTALITY IN SELECTED COUNTRIES

R. A. M. CASE

It would be difficult to make a detailed comparison of either the mortality or morbidity experience from cancer of the lungs over a range of countries because a consistent system of recording results has not been used, and many of the studies refer to different dates.

The United Nations and the World Health Organization have for some years been trying to escape from this demographic impasse by publishing death and population data from countries willing to co-operate. These data are published in two series of annual reports, the Demographic Yearbook (United Nations) and the Annual Epidemiological and Vital Statistics (World Health Organization).

Case and Harley (1958) prepared a series of age-specific death rate tables for as many countries as had provided quinary-grouped age-specific data for both population and cancer mortality by site. The tables are for the grouped three-year period 1951–53 and include twenty-one countries. The breakdown by site is necessarily in rather large groupings. One of these groupings is 'Cancer of the Respiratory System' (International Statistical Classification Nos 160–165), and these data are shown in Tables IV and V.

The figures should be interpreted with great caution, for not only does the quality of the raw data vary from country to country, but the fraction of the site classification which is not due to cancer of the lungs (less than 5 per cent in England and Wales) may vary widely from country to country. Each array of age-specific death rates should be regarded as having evolved in the way described in Appendix I (pp. 272–274) and not regarded as a sequential series expressing solely the age of the individuals. These sets of international tables are presented as reference data, and it is outside the scope of this chapter to attempt to interpret them.

TABLE IV

Contemporary Arrays of Age-specific Death Rates for Cancer of the Respiratory System (I.S.C. Nos. 160–165) for 21 Selected Countries. 1951–53. Males.

Age (years)	Australia*	Canada†	Chile	Denmark	Finland	France	Germany (Federal Republic)
25–	0·009	0·008	0·013	0·004	0·014	0·010	0·008
30–	0·014	0·011	0·014	0·009	0·011	0·014	0·015
35–	0·025	0·040	0·019	0·034	0·062	0·050	0·031
40–	0·079	0·084	0·082	0·074	0·182	0·106	0·101
45–	0·199	0·188	0·152	0·272	0·531	0·318	0·305
50–	0·383	0·443	0·254	0·534	1·100	0·612	0·714
55–	0·672	0·730	0·367	0·942	2·061	0·864	1·198
60–	0·975	0·914	0·543	1·059	2·622	1·097	1·344
65–	1·304	1·282	0·753	1·004	3·378	1·197	1·409
70–	1·381	1·226	0·738	1·055	2·952	1·256	1·349
75–	1·244	1·268	0·877	1·140	2·677	1·164	1·353
80–84	0·833	1·081	0·563	1·060	2·367	1·035	0·930
All ages	0·204	0·202	0·075	0·236	0·419	0·285	0·315

Age (years)	Ireland (Republic)	Israel (Jewish Population)	Italy	Japan	Netherlands	New Zealand‡	Norway
25–	0·007	0·006	0·008	0·004	0·010	0·005	0·005
30–	0·048	0·025	0·021	0·007	0·021	0·000	0·015
35–	0·049	0·027	0·038	0·017	0·065	0·030	0·011
40–	0·170	0·052	0·121	0·032	0·170	0·088	0·047
45–	0·328	0·127	0·310	0·068	0·348	0·272	0·122
50–	0·511	0·286	0·562	0·127	0·711	0·450	0·247
55–	0·795	0·464	0·714	0·213	1·192	1·066	0·358
60–	0·831	0·567	0·733	0·311	1·364	1·093	0·465
65–	0·923	1·545	0·665	0·471	1·601	1·487	0·501
70–	0·753	1·184	0·659	0·435	1·850	1·544	0·409
75–	0·748	—	0·616	0·413	1·665	1·600	0·590
80–84	0·796	—	—	—	1·322	1·125	0·467
All ages	0·215	0·112	0·164	0·048	0·306	0·268	0·108

Age (years)	Sweden	Switzerland	Union of South Africa (European Population)	United Kingdom			United States
				England and Wales	Northern Ireland	Scotland	
25–	0·004	0·004	0·010	0·015	0·022	0·021	0·008
30–	0·011	0·002	0·003	0·039	0·037	0·045	0·017
35–	0·020	0·058	0·038	0·109	0·115	0·149	0·049
40–	0·034	0·117	0·076	0·252	0·183	0·291	0·127
45–	0·114	0·328	0·224	0·591	0·416	0·752	0·293
50–	0·247	0·679	0·632	1·243	0·719	1·459	0·568
55–	0·464	1·062	0·919	1·989	1·028	2·006	0·929
60–	0·578	1·312	1·413	2·502	1·209	2·423	1·253
65–	0·495	1·599	1·788	2·911	1·260	2·612	1·390
70–	0·623	2·173	1·699	2·653	1·453	2·096	1·320
75–	0·483	1·972	1·504	2·266	0·713	2·015	1·261
80–84	0·432	2·036	1·223	1·714	0·944	1·380	1·027
All ages	0·131	0·345	0·226	0·617	0·279	0·572	0·263

Age-specific death rates per thousand living per year
Based on figures including non-civilians.
* Excluding full-blood aboriginals.
† Excluding Yukon and N.W. Territories.
‡ Excluding Maoris
— Figures not available.

Table V

Contemporary Arrays of Age-specific Death Rates for Cancer of the Respiratory System (I.S.C. Nos. 160–165) for 21 Selected Countries. 1951–53. **Females.**

Age (years)	Australia*	Canada†	Chile	Denmark	Finland	France	Germany (Federal Republic)
25–	0·003	0·005	0·001	0·006	0·006	0·004	0·003
30–	0·005	0·008	0·010	0·009	0·016	0·007	0·011
35–	0·012	0·013	0·020	0·021	0·013	0·022	0·014
40–	0·027	0·035	0·036	0·041	0·033	0·033	0·031
45–	0·036	0·048	0·045	0·064	0·059	0·051	0·052
50–	0·068	0·074	0·089	0·072	0·114	0·082	0·094
55–	0·126	0·109	0·168	0·147	0·183	0·124	0·127
60–	0·145	0·165	0·196	0·259	0·192	0·167	0·195
65–	0·199	0·271	0·309	0·265	0·334	0·199	0·277
70–	0·264	0·261	0·320	0·360	0·518	0·265	0·325
75–	0·342	0·385	0·385	0·337	0·540	0·287	0·384
80–84	0·466	0·400	0·352	0·430	0·290	0·284	0·323
All ages	0·047	0·044	0·033	0·065	0·064	0·065	0·062

Age (years)	Ireland (Republic)	Israel (Jewish Population)	Italy	Japan	Netherlands	New Zealand‡	Norway
25–	0·017	0·011	0·004	0·002	0·005	0·005	0·005
30–	0·007	0·007	0·009	0·006	0·009	0·005	0·000
35–	0·047	0·018	0·015	0·013	0·014	0·010	0·005
40–	0·054	0·048	0·035	0·022	0·027	0·037	0·008
45–	0·140	0·050	0·053	0·037	0·039	0·049	0·033
50–	0·138	0·048	0·074	0·061	0·061	0·083	0·057
55–	0·204	0·180	0·119	0·078	0·111	0·225	0·139
60–	0·231	0·239	0·157	0·121	0·155	0·126	0·147
65–	0·275	0·290	0·203	0·143	0·245	0·147	0·198
70–	0·301	0·646	0·231	0·151	0·257	0·296	0·305
75–	0·213	—	0·276	0·148	0·380	0·288	0·263
80–84	0·205	—	—	—	0·348	0·585	0·281
All ages	0·073	0·046	0·045	0·021	0·046	0·052	0·049

Age (years)	Sweden	Switzerland	Union of South Africa (European Population)	United Kingdom			United States
				England and Wales	Northern Ireland	Scotland	
25–	0·003	0·005	0·000	0·007	0·013	0·009	0·003
30–	0·005	0·006	0·007	0·017	0·021	0·030	0·007
35–	0·004	0·008	0·035	0·033	0·057	0·045	0·016
40–	0·033	0·014	0·048	0·058	0·036	0·067	0·031
45–	0·037	0·053	0·111	0·097	0·055	0·120	0·055
50–	0·067	0·059	0·098	0·148	0·141	0·179	0·087
55–	0·139	0·095	0·171	0·222	0·175	0·286	0·125
60–	0·187	0·162	0·271	0·317	0·277	0·370	0·176
65–	0·254	0·172	0·357	0·392	0·415	0·393	0·233
70–	0·360	0·316	0·236	0·424	0·213	0·488	0·307
75–	0·302	0·322	0·602	0·511	0·239	0·642	0·394
80–84	0·231	0·370	0·472	0·480	0·309	0·582	0·397
All ages	0·061	0·053	0·059	0·111	0·072	0·119	0·053

Age-specific death rates per thousand living per year
Based on figures including non-civilians.
* Excluding full-blood aboriginals.

† Excluding Yukon and N.W. Territories.
‡ Excluding Maoris.
— Figures not available.

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25–	0·009	0·008	0·013	0·004	0·014	0·010	0·008
30–	0·014	0·011	0·014	0·009	0·011	0·014	0·015
35–	0·025	0·040	0·019	0·034	0·062	0·050	0·031
40–	0·079	0·084	0·082	0·074	0·182	0·106	0·101
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50–	0·383	0·443	0·254	0·534	1·100	0·612	0·714
55–	0·672	0·730	0·367	0·942	2·061	0·864	1·198
60–	0·975	0·914	0·543	1·059	2·622	1·097	1·344
65–	1·304	1·282	0·753	1·004	3·378	1·197	1·409
70–	1·381	1·226	0·738	1·055	2·952	1·256	1·349
75–	1·244	1·268	0·877	1·140	2·677	1·164	1·353
80–84	0·833	1·081	0·563	1·060	2·367	1·035	0·930
All ages	0·204	0·202	0·075	0·236	0·419	0·285	0·315

Age (years)	*Ireland (Republic)*	*Israel (Jewish Population)*	*Italy*	*Japan*	*Netherlands*	*New Zealand‡*	*Norway*
25–	0·007	0·006	0·008	0·004	0·010	0·005	0·005
30–	0·048	0·025	0·021	0·007	0·021	0·000	0·015
35–	0·049	0·027	0·038	0·017	0·065	0·030	0·011
40–	0·170	0·052	0·121	0·032	0·170	0·088	0·047
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60–	0·831	0·567	0·733	0·311	1·364	1·093	0·465
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75–	0·748	—	0·616	0·413	1·665	1·600	0·590
80–84	0·796	—	—	—	1·322	1·125	0·467
All ages	0·215	0·112	0·164	0·048	0·306	0·268	0·108

Age (years)	*Sweden*	*Switzerland*	*Union of South Africa (European Population)*	*United Kingdom*			*United States*
				England and Wales	*Northern Ireland*	*Scotland*	
25–	0·004	0·004	0·010	0·015	0·022	0·021	0·008
30–	0·011	0·002	0·003	0·039	0·037	0·045	0·017
35–	0·020	0·058	0·038	0·109	0·115	0·149	0·049
40–	0·034	0·117	0·076	0·252	0·183	0·291	0·127
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50–	0·247	0·679	0·632	1·243	0·719	1·459	0·568
55–	0·464	1·062	0·919	1·989	1·028	2·006	0·929
60–	0·578	1·312	1·413	2·502	1·209	2·423	1·253
65–	0·495	1·599	1·788	2·911	1·260	2·612	1·390
70–	0·623	2·173	1·699	2·653	1·453	2·096	1·320
75–	0·483	1·972	1·504	2·266	0·713	2·015	1·261
80–84	0·432	2·036	1·223	1·714	0·944	1·380	1·027
All ages	0·131	0·345	0·226	0·617	0·279	0·572	0·263

Age-specific death rates per thousand living per year.
Based on figures including non-civilians
* Excluding full-blood aboriginals.

† Excluding Yukon and N W Territories
‡ Excluding Maoris
— Figures not available

SECTION TWO

PRESENT KNOWLEDGE OF THE CAUSATION OF CARCINOMA OF THE LUNG

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INTRODUCTION

RICHARD DOLL

IT must be admitted that the 'cause' is not yet known for any type of cancer, if by 'cause' is meant that which is always and unconditionally followed by the appearance of the corresponding effect But, from a practical point of view, it is not helpful to limit the use of the term to this sense, since it is not necessary to have so complete a knowledge before a disease can be prevented It is generally more useful to regard the causation of a disease as the sum of all those processes which under suitable conditions will lead to its occurrence It may be possible perhaps to interrupt these processes at several stages and it has sometimes been found that a disease can be effectively prevented through knowledge of one or other of them before knowledge is obtained of the nature of the final cause The exact physical and chemical changes which induce a cell in the bronchial mucosa to become malignant are not known; but, in the course of the last eighty years, much has been learnt of the conditions under which these changes are most frequently brought about and it is these conditions which may usefully be regarded as the causes of lung cancer

The search for causes has been facilitated by the striking differences in the mortality from lung cancer which have been recorded at different times, in different parts of the world and between men and women In England and Wales the crude death rate from the disease has increased nearly 50 times in the last 50 years and it has been shown in Chapter II that much of this rise (though not all) is likely to have been due to a real increase in incidence. Both sexes have been affected, but the rates of increase have been unequal and the ratio between the death rates in men and in women has increased from approximately 1½ to 1 at the beginning of the century to nearly 7 to 1 in 1955 In other countries similar changes have taken place, but the extent of the increase has been less marked and, except in Finland and Austria, the mortality has nowhere reached much more than half that recorded in Britain. Substantial differences have, moreover, been recorded between different regions within a country and, wherever data have been obtained, it has invariably been found that the mortality is greater in the large towns than in rural areas. These facts have directed attention to the possibility that environmental factors might be responsible for the production of much of the disease and—in particular—to the possible roles of industrial hazards, atmospheric pollution and the smoking of tobacco.

SIGNIFICANCE OF HISTOLOGICAL TYPE

Not all types of lung cancer are necessarily equally related to the same environmental factors. The sex ratio, for example, varies with the different

We are constantly deluded by language. We say a person dies of cancer; . . . The truth must be that a person dies of the causes of cancer; and the cancer is not the cause, but the mode of dying.

Lambe, William (1815). *Additional Reports on the Effects of a Peculiar Regimen in cases of Cancer, Scrofula, Consumption, Asthma and other Chronic Diseases, p.* 411. *London. Printed for J. Mawman,* 39 *Ludgate Street.*

CHAPTER V

SPECIFIC INDUSTRIAL CAUSES

RICHARD DOLL

THE classical method which led to the discovery of a specific cause of cancer was the observation that a high incidence of one type of cancer occurred among men employed in a particular occupation. This method of study has been very fruitful in the case of cancer of the lung; five industries have already been shown to carry exceptional risks of the disease and several others are under suspicion.

RADIOACTIVE ORES

The first industry to be implicated was mining in the mountains of Saxony and Bohemia For at least 500 years the miners of Schneeberg and Jachymov were victims of a chronic pulmonary disease which is believed to have been the cause of between 44 and 75 per cent of all their deaths. The disease was first recognised to be primary cancer of the lung nearly 80 years ago by Harting and Hesse (1879) and since then, according to Hueper (1956), 625 cases have been reported. Nearly 90 per cent of all tumours among the miners arose from the bronchi and in 1939 Peller estimated that the miners of Jachymov were nearly 30 times as liable to develop the disease as adult men in Vienna; both Peller's and Šikl's (1950) data suggest that the mortality from lung cancer among them was approximately 1 per cent a year. As in nearly all types of industrial cancer, the time between first exposure and the appearance of the disease was long Šikl (1950) found that the average induction time was 17 years and that no cases appeared with less than 13 years' exposure Histologically the tumours were almost invariably squamous, oat-cell or undifferentiated (Schmorl 1928; Hueper 1942; Šikl 1950).

In the course of history the mines have been worked for many different materials—for silver, nickel, cobalt, bismuth and arsenic, for radium and finally for uranium. It was the ore from Jachymov which provided the material from which the Curies, in 1898, isolated radium chloride and it was the high content of radio-activity which, until recently, distinguished these mines from all others. The suggestion that radioactivity might be the cause of the disease first appeared in the medical literature in 1921 when Margarete Uhlig, herself a native of Schneeberg, wrote that she had seen it made, in an article 'by a layman'. The mean concentration of radon in the air of the mines was certainly high According to Evans (1950) it was equivalent to an activity of 3×10^{-9} curies per litre and other estimates have set the average 10 times higher (Mitchell 1945) Evans calculated that an activity of 3×10^{-9} curies per litre would have

histological types and the proportions belonging to each type vary with age. Kreyberg (1956) has studied Norwegian material in great detail from this point of view and has found that the male preponderance is confined to cases of squamous, large cell and small cell carcinoma (corresponding in general to the sum of the squamous, oat cell and anaplastic tumours described by British pathologists). These tumours also had a characteristic age distribution with a maximum incidence in the fifth and sixth decades and have been responsible for the greater part of the recorded increase in male mortality;* the patients have, moreover, come predominantly from the towns. Kreyberg concluded that these types of tumour were histological variants of an oncological entity and that the majority of the cases were brought about by new environmental factors to which men resident in towns were principally exposed.

The remaining primary epithelial lung tumours formed a more heterogeneous group. All showed an equal sex ratio and, as a group, all occurred in patients who came equally from all parts of the country. The adenocarcinomas, however, occurred with increasing frequency with advancing years, while the adenomas and salivary gland tumours occurred equally at all ages and the bronchiolar cell carcinomas were too uncommon for any characteristic age distribution to be recognised There is, in Kreyberg's view, no reason to suppose that any of these histological types have increased in incidence. It may be that some (for example, the adenomas and salivary gland tumours) are of developmental origin. Others may, perhaps, be related to environmental factors; but, if so, the factors are likely to be entirely different from those responsible for the more common squamous, oat-cell and anaplastic varieties

The incidence of lung cancer in Norway is lower than in most other countries for which the incidence may be estimated with reasonable accuracy (see Table IV of Chapter III) and it does not necessarily follow that Kreyberg's conclusions are invariably applicable In a survey of data from 8 countries, however, Ringertz (1955) found that the mortality from adenocarcinoma of the lung appeared to be about equal in both sexes and, although other data have not been studied in the same detail, the trend of the observations is generally similar (for example, Lickint 1953). Kreyberg's conclusions may, therefore, be regarded as providing useful working hypotheses.

* This should not be regarded as implying a specific 'cancer age' for this or any other type of tumour; the significance of the variation in incidence with age is discussed fully in Chapter II and Appendix I

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delivered a dose of approximately 0·5 *roentgen-equivalent-man* per working day to the epithelium of the larger bronchi, so that with an average induction time of 17 years the total dose would have been of the order of 3,000 *roentgen-equivalent-man*. Shapiro (1954), however, and Turner (personal communication) independently pointed out that Evans ignored the effect of the particulate matter in the air which carried the breakdown products of radon and they estimate that the total dose received by some parts of the bronchi is likely to have been several times higher Since persons who suffered from chronic radium poisoning and who developed bone sarcoma are estimated to have received local doses of about 35,000 *roentgen-equivalent-man* (Evans 1950), the physical data are reasonably consistent with the hypothesis that the Jachymov cancers were due to exposure to radon and this view is now widely—though not universally—accepted. It is supported by the observations of Rajewsky, Schraub and Kahlau (1943) who exposed mice continuously to various doses of radon and found that 10 out of 12 animals exposed to a concentration of $1{\cdot}16 \times 10^{-6}$ curies per litre developed adenomas and one developed a bronchial adenocarcinoma One adenoma was found in the controls. It has, however, now been shown conclusively that radioactive materials (cerium oxide and plutonium oxide) are capable of producing true bronchial cancers in the rat (Lisco and Finkel 1949; Lisco, personal communication).

The fact that a high proportion of the miners suffered from silicosis may have facilitated the effect of the radiation, since it has been shown that, in some species, cancer can be induced by radiation more easily when non-specific inflammation is also present (Burrows and Clarkson 1943).

Whether similar cases have been produced in other mines is unknown. The two high-grade uranium mines at Shinkolobwe in the Belgian Congo and Port Radium, Canada, have been exploited long enough for an effect to appear, but the conditions of work have been such that the collection of data has not been easy At Port Radium, for example, the mines have been worked by small groups of men who, because of the arduous conditions of life in the Arctic, have stayed only for one or two seasons. In the more modern mines the uranium content of the ore is generally much lower, so that even when they have been worked previously for other metals (*e.g*, the South African gold mines) no significant risk has been detected. Some of the mines of the Colorado plateau may be exceptions, as the radon concentration in these mines has been estimated to be similar to that in the Schneeberg mines (Shapiro 1954) Many of the mines in Colorado and Montana have been worked for copper and it is possible that radioactivity accounts for some of the high mortality from lung cancer reported from the Montana area (Table VI), the data are, however, inadequate for any conclusion about the cause to be reached.

Nickel Refining

The only form of lung cancer to be officially prescribed in Britain as an industrial disease is that which occurs among men employed at a nickel refinery and exposed to 'nickel produced by decomposition of a gaseous nickel

TABLE VI

*Lung Cancer Mortality in 4 Counties of Montana, 1947–48**

Population	County	Major industry	Number of cases of lung cancer		Annual lung cancer rate per 100,000	
			M	F	M	F
13,627	Deer Lodge	Copper smelting	21	0	146	0
53,207	Silver Bow	Copper mining	27	2	49	4
41,499	Cascade	Copper mining and smelting	20	5	46	12
18,269	Gallatin	Agriculture	1	0	5	0

The crude death rate for lung cancer among white males in the U S.A. in 1947 was 11 per 100,000.
* After Lull and Wallach cited by Hueper (1956)

compound'. The detailed evidence on which the prescription was based has, however, not been published Reports of a small number of cases among the workers were published by Amor (1939) and altogether 93 cases of lung cancer and 52 cases of nasal cancer were notified between the years 1923 and 1950 (Chief Inspector of Factories 1952). Some of the nasal cancers arose from the maxillary antrum but the majority arose from the ethmoid and, in view of the extreme rarity of this type of cancer,* the large number of cases notified is, in itself, sufficient evidence of the existence of a specific risk The position is, however, different with a common condition and a detailed estimate of the expected mortality is necessary before the existence of a special risk of lung cancer can be accepted. Such an estimate has been made from an analysis of the numbers of deaths attributed to different causes in the area in which the refinery is situated (Doll 1958). These data are summarized in Table VII, which shows that between the years 1938 and 1956 26 per cent of all deaths among the nickel workers were attributed to lung cancer and 10 per cent were attributed to nasal cancer. If the mortality of nickel workers from other causes of death was equal to that of other men in the same area and the expected number of deaths from lung cancer is taken to be the number which would have occurred if the proportion of deaths attributed to lung cancer were the same as the proportion attributed to the disease among the other workers, the observed number of cases of lung cancer would appear to have been 9 times the expected (75 against 8·5)

According to Morgan (1953) the risk of cancer was eliminated with the reorganisation of the process in 1924. Whether this is so is, however, not yet certain The annual number of deaths attributable to the process remains high, but the average age at death has increased and there is no evidence that any excess of cases has occurred among men first employed after the reorganisation.

* Figures are not available for the mortality from ethmoid cancer in Britain, but it forms only a small proportion of the total deaths recorded from all types of nasal cancer and cancer of the middle ear (International List No 160) which amount to only 5 per million men annually.

TABLE VII

Number of Men Dying in Two Administrative Districts of Glamorganshire, 1938–56, Subdivided by Cause of Death, and Last Employment

Cause of death	Industry						All occupations
	Nickel works		Colliery		Other		
	Number of deaths	Percentage all deaths	Number of deaths	Percentage all deaths	Number of deaths	Percentage all deaths	Number of deaths
Cancer of the lung	75	25 6	31	1 4	189	3 5	295
Cancer of the nose	29	9 9	3	0 1	5	0 1	37
Other causes	189	64 5	2,154	98 4	5,190	96 4	7,533
All causes	293	100 0	2,188	99 9	5,384	100 0	7,865

The British refinery used a process of purification in which the gas, nickel-carbonyl ($Ni(Co)_4$), is formed from finely divided nickel and water gas. The gas readily decomposes and nickel must be presumed to be deposited in a highly active form when the gas comes in contact with the respiratory mucosa. No cases have been reported from other refineries, which use other processes, in Canada, Germany and the U S.A., and this has led to the conclusion that nickel deposited by the gas is the active agent. Support for this view is provided by Hueper (1951, 1952) who induced cancer in rats—but not in other animals—by the injection of pure metallic nickel powder in lanoline into the marrow cavity of the femur, the pleural cavity and the nasal sinuses. Five cases of lung cancer have, however, occurred in a few years among workers at a small refinery in Norway in which an electrolytic process is used (Løken 1950; Goldblatt and Goldblatt 1956), so that the exact nature of the carcinogen still remains in doubt.

CHROMATES

The first reports of the occurrence of lung cancer among chromate workers came from Germany (Pfeil 1935; Alwens, Bauke and Jonas 1936). At least 62 German cases are now known to have occurred (Baetjer 1950), but the size of the population at risk is not known with accuracy and the existence of a specific industrial hazard was not established until Machle and Gregorius (1948) and later Brinton, Frasier and Koven (1952) obtained data from 7 chromate plants in the U.S A. These showed that the mortality from lung cancer among the employees was some 30 times greater than would have been expected from either the national mortality data or the records of other industrial workers of corresponding ages. In contrast, the mortality from other types of cancer among the chromate workers was similar to that recorded for all men throughout the country.

At that time there was no suspicion of a risk in Britain and attempts were made to explain the different experiences in the three countries by differences

in the technique of manufacture. A preliminary clinical and radiological examination of 724 men employed in the 3 British plants engaged in the manufacture of chromates from chromite ore revealed only one case (Bidstrup 1951) In the next 6 years, however, Bidstrup and Case (1956) discovered 14 further cases. Of these, 12 occurred among the men who had previously been x-rayed by Bidstrup; all the affected men had died and their deaths had all been certified as due to lung cancer. Of the other cases, one was found at a repeat x-ray examination at the end of the inquiry and the second occurred in an employee who had not been included at the initial examination Had the men who were studied experienced the same mortality from lung cancer as other men of the same ages in Britain, the number of deaths from lung cancer would have been about 3 (actual calculated number 3·3) and the observed mortality was, therefore, about 4 times the normal. In contrast, the mortality from other causes was close to normal; 9 deaths were recorded from other types of cancer against 7·3 expected and 38 deaths from all other causes against 36·3 expected. The men were, therefore, not unhealthy in general and the excess mortality from lung cancer must be regarded as evidence of a specific hazard.

At first sight it might appear that the hazard in Britain was much smaller than in the U.S A The 'normal' mortality with which the mortality of the American workers was compared was, however, recorded at a time when the normal mortality from lung cancer was less than half that recorded during the period of Bidstrup and Case's study and 'normal' American mortality is, moreover, only about half the British That the extent of the risk has not been dissimilar in the two countries is illustrated by comparison of the proportions of the total deaths which were attributed to the disease Out of 193 deaths from all causes Machle and Gregorius found 42 attributed to lung cancer, whereas Bidstrup and Case found 12 out of 59; if the deaths from lung cancer which were attributable to non-industrial causes are excluded it appears that the specific hazards were responsible for 21 per cent of the total deaths in America and for 15 per cent in Britain

Evidence of the exact nature of the substance responsible for the induction of the disease is conflicting The ore is a ferrous ore ($FeO.Cr_2O_3$) which contains 40–50 per cent chromium and small amounts of alumina and silica. No cases have been reported among miners of the ore, but important risks of cancer can easily be overlooked and it would be unwise to regard the ore as necessarily innocuous. Apart from men engaged in the manufacture of chromates from the crude ore, the only other group among which cases have been reported consists in men engaged in the manufacture from dichromates of chrome pigments, *i e*, chromates of lead and zinc (Gross and Kölsch 1943) Machle and Gregorius, on the other hand, found no cases of lung cancer in the one American plant in which the only important exposure was to dichromates and chromic acid Apart from two cancers in rabbits which followed the intra-femoral injections of metallic chromium (Schinz and Uhlinger 1941), animal experiments have so far proved negative. The consensus of present opinion is that the carcinogen will probably prove to be trivalent chromium in the form of acid-soluble-water-insoluble compounds.

ASBESTOS

The first case of lung cancer to be described in association with asbestosis was reported by Lynch and Smith (1935) in the U.S.A. Since then over 60 cases have been reported from Britain, Canada, Germany and the U.S.A.—the majority from Britain. That the association was not just coincidental was indicated by comparison of the incidence of lung cancer at autopsy in cases of asbestosis and cases of silicosis. Merewether (1949) found that lung cancer was reported in 13·2 per cent of subjects with asbestosis (31 out of 235) and in 1·3 per cent of subjects with silicosis (91 out of 6,884) and Gloyne (1951), on personal examination, found corresponding incidences of 14·1 and 6·9 per cent (17 out of 121 and 55 out of 796). It should, moreover, be noted that women formed an appreciable proportion of the subjects with asbestosis and that the incidence among men with the disease was even higher—17·2 per cent in Merewether's series and 19·6 per cent in Gloyne's. Since all—or almost all—silicotics are likely to have been men, the contrast between subjects of the same sex is likely to have been somewhat greater than that actually reported for both sexes together. These results are most readily explained if asbestos predisposes to the development of lung cancer and this explanation was subsequently borne out by Doll's (1955) study of the mortality recorded among asbestos workers. He studied 113 men who had worked for 20 or more years in places where they were liable to be exposed to asbestos dust and found that between 1922 and 1953 39 died, whereas on the basis of the mortality rates suffered by men of the same ages in the whole population only 15·4 deaths would have been expected. Of the 39 deaths 11 were due to lung cancer, whereas less than 1 (0·8) would have been expected. All the cases of lung cancer were confirmed histologically and all were associated with asbestosis. Precautions to prevent the dissemination of dust greatly reduced the amount to which the men were exposed from 1933 onwards and the incidence of the disease has become progressively less as the number of years during which the men were exposed to the pre-1933 conditions has diminished. It is evident, therefore, that lung cancer is a specific industrial hazard of asbestos workers, but that with scrupulous attention to the control of dust the risk may be greatly reduced and may, perhaps, be eliminated.

The fibrils of asbestos consist of giant molecules of polymerised silico-oxygen tetrahedra arranged in chains or bands. In the case of Canadian asbestos, the silica is present as hydrated magnesium silicate containing 6 per cent of iron oxide; in other, industrially less important, types the silicates may be calcium and magnesium or sodium and iron. Animal experiments have, in general, failed to show any significant carcinogenic activity from asbestos fibres and the mode of production of the disease is uncertain. In Hueper's view (1957a) the activity may result from the occurrence of the material in the form of a linear polymer and the mechanism by which cancer is produced may be similar to that with various polymerised carbon compounds, which have been shown to be carcinogenic experimentally.

COAL TAR

The combustion and distillation products of coal provide a rich source of carcinogens and have, for many years, been known to be capable of causing cancer of the skin among men whose work brings them into direct contact with the material. It would, therefore, not be surprising if men who inhaled the fumes and dust from tar were liable to develop lung cancer That there is, in fact, such a risk is shown by evidence from Britain, Canada and Japan

The Japanese observations were first reported in 1936 (Kuroda and Kawahata 1936; Kuroda 1937; Kawahata 1938). Twenty-one cases of lung cancer were recognised among gas generator workers and ex-workers of the Yawata Steel Works between the years 1931 and 1937 and there can be little doubt that this indicates an exceptionally high incidence Detailed epidemiological data are not available, but lung cancer was at that time a rare disease in Japan and it is striking that, during the years 1931–35, 12 deaths from lung cancer were observed among the gas workers, while no such deaths were observed among the other workers. Among the gas workers lung cancer accounted for 80 per cent of all cancer deaths (12 out of 15). The gas workers appear to have constituted about 2½ per cent of the total employees (*i e*, about 500 out of 20,000) and the mortality from other types of cancer was not very dissimilar from that among other employees of the works (3 out of 500 and 49 out of 19,000) The men worked immediately above the ovens and when they stirred the coal, yellow-brown gas streamed over them through the opening

In Britain a high mortality among various groups of gas and tar workers was noted by Kennaway and Kennaway (1947), from an analysis of the occupations given on the death certificates of men dying of lung cancer between 1921 and 1938. Of the 56 occupations studied there were 10 in which the employees might be supposed to have special exposure to coal-gas and tar In 9 the estimated mortality from lung cancer was above the average for the whole male population and 4 of these were among the 5 occupations with the highest mortalities (Table VIII). Subsequently Doll (1952) studied the causes of death

TABLE VIII

Occupations with the Highest Mortality from Lung Cancer
*(56 selected occupations, 1921–38)**

Occupation	*Number of deaths registered*	*Registered deaths as a percentage of the number of deaths expected*
Labourers, patent fuel works	3	571
Gas stokers and coke oven chargers	85	284
Gas producer men	12	202
Metal grinders	39	176
Gas works foremen and inspectors	25	174

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Asbestos

The first case of lung cancer to be described in association with asbestosis was reported by Lynch and Smith (1935) in the U.S.A. Since then over 60 cases have been reported from Britain, Canada, Germany and the U S A—the majority from Britain. That the association was not just coincidental was indicated by comparison of the incidence of lung cancer at autopsy in cases of asbestosis and cases of silicosis. Merewether (1949) found that lung cancer was reported in 13·2 per cent of subjects with asbestosis (31 out of 235) and in 1·3 per cent of subjects with silicosis (91 out of 6,884) and Gloyne (1951), on personal examination, found corresponding incidences of 14·1 and 6·9 per cent (17 out of 121 and 55 out of 796). It should, moreover, be noted that women formed an appreciable proportion of the subjects with asbestosis and that the incidence among men with the disease was even higher—17·2 per cent in Merewether's series and 19·6 per cent in Gloyne's. Since all—or almost all—silicotics are likely to have been men, the contrast between subjects of the same sex is likely to have been somewhat greater than that actually reported for both sexes together. These results are most readily explained if asbestosis predisposes to the development of lung cancer and this explanation was subsequently borne out by *Doll's (1955) study of the mortality recorded* among asbestos workers He studied 113 men who had worked for 20 or more years in places where they were liable to be exposed to asbestos dust and found that between 1922 and 1953 39 died, whereas on the basis of the mortality rates suffered by men of the same ages in the whole population only 15·4 deaths would have been expected Of the 39 deaths 11 were due to lung cancer, whereas less than 1 (0·8) would have been expected. All the cases of lung cancer were confirmed histologically and all were associated with asbestosis. Precautions to prevent the dissemination of dust greatly reduced the amount to which the men were exposed from 1933 onwards and the incidence of the disease has become progressively less as the number of years during which the men were exposed to the pre-1933 conditions has diminished. It is evident, therefore, that lung cancer is a specific industrial hazard of asbestos workers, but that with scrupulous attention to the control of dust the risk may be greatly reduced and may, perhaps, be eliminated.

The fibrils of asbestos consist of giant molecules of polymerised silico-oxygen tetrahedra arranged in chains or bands. In the case of Canadian asbestos, the silica is present as hydrated magnesium silicate containing 6 per cent of iron oxide; in other, industrially less important, types the silicates may be calcium and magnesium or sodium and iron. *Animal experiments* have, in general, failed to show any significant carcinogenic activity from asbestos fibres and the mode of production of the disease is uncertain In Hueper's view (1957a) the activity may result from the occurrence of the material in the form of a linear polymer and the mechanism by which cancer is produced may be similar to that with various polymerised carbon compounds, which have been shown to be carcinogenic experimentally.

among the employees of a small English factory in which an arsenical powder was prepared from a solution of sodium arsenite (Hill and Faning 1948) Examination of the death entries in the offices of the local Registrars of Deaths showed that 75 male employees of the factory had died between 1910 and 1943 The causes of these deaths were compared with the causes of deaths recorded for other male manual workers resident in the same area during the same period, and it was found that the proportion of deaths attributed to cancer was higher for the factory workers than for the other workers (29 3 per cent against 12·9 per cent)—and was higher still among those men who were most likely to come into direct contact with the dust (*i e.*, 39·0 per cent) The high proportion of cancer deaths was largely due to an excess of deaths from cancer of two sites—respiratory system and skin Out of 22 cancer deaths, 3 were attributed to cancer of the skin and 7 to cancer of the respiratory system (lung 5, mediastinum 1 and larynx 1), whereas Hill and Faning estimated that the numbers expected would have been no more than 0·12 and 1·01 respectively Environmental studies carried out by Perry and his colleagues (Perry *et al* 1948) showed that very large quantities of arsenic might be present in the air—ranging, at mouth height, in one part of the factory, from 310 µg. of arsenic per m^3 to over 4,000 µg with a mean of approximately 1,000 µg Masks were worn, but apparently without much effect, as large quantities of arsenic were found in the urine and hair of the workers and the majority of the chemical workers were grossly pigmented, approximately one-third of them had warts

It seems probable, therefore, that exposure to inorganic arsenic in the air is capable of producing lung cancer, if the amount present is sufficient to produce gross evidence of arsenicism In the absence of such evidence, however, *it would seem most unlikely that the amount of arsenic inspired is sufficient* to account for the high incidence of the disease among groups of workers not primarily concerned with the manufacture of arsenic compounds

IRON

The siderosis caused by pulmonary retention of Fe_2O_3 or $Fe_3O_4.H_2O$ is usually considered an innocuous form of pneumoconiosis which does not cause disability There is, however, some evidence to suggest that under certain conditions (particularly in association with silicosis) it may lead to a somewhat higher incidence of lung cancer Turner and Grace (1938) found that foundry workers, smiths and metal grinders had a mortality from lung cancer higher than that of any other occupational group in Sheffield and metal grinders were also found to have suffered a high mortality from lung cancer in Kennaway and Kennaway's (1947) study They found that 39 deaths were recorded among metal grinders in England and Wales between 1921 and 1938, whereas they estimated that the number expected on the basis of national rates (allowing for differences in age distribution) was 22·2 In this study the ratio of observed to expected deaths for metal grinders (1·76 to 1) was exceeded only by 3 groups of gas or pitch workers out of the 56 occupational groups studied (see Table VIII and p 51) 'Metal moulders and casters' and 'iron foundry furnacemen and

among 2,071 male pensioners of a London gas company and found that the number of deaths from lung cancer was approximately double that expected by comparison with male inhabitants of London of the same ages (25 against 13·8 expected). The excess is small, but the investigation covered a multiplicity of occupations and it is probable that the risk was substantially greater for those men who were most closely concerned with the production process. Reid and Buck (1956), on the other hand, were unable to find any evidence of an increased risk among men employed in an apparently similar occupation—namely, men in coking plants producing metallurgical coke.

In Canada, Sutherland (personal communication) found that the mortality from respiratory cancer among men who had worked in the retort house of one particular works was some 15 times greater than that recorded for the *general population of the district; out of 19 cancer deaths 9 (i.e., 47 per cent)* arose in the respiratory system The works was one in which horizontal retorts continued to be used and, in the operation of these retorts, the men were exposed from time to time to considerable quantities of hot gas and tar fumes. Employees of the works who had never been employed in the retort house showed no excess mortality from respiratory cancer; and neither did employees at another works where the retorts had been modernised.

Quantitative estimates of the amount of carcinogens likely to be inspired are not yet available. Measurements in a retort house containing vertical retorts at one gas works have, however, shown that the amount of 3:4-benzpyrene in the air may be 5 to 10 times greater than in the general atmosphere of a large English town (Hughes and Somerville, personal communication) and it is reasonable to presume that this substance is the principal carcinogenic agent The amount likely to be present must be expected to vary greatly with different types of retort and with differences in the method of operation and this may partly account for the lack of uniformity in the observations

Arsenic

The occurrence of cancer of the skin in patients who had received prolonged arsenical medication and in workers exposed to arsenical dust, and the observation that the latter group were also subject to perforation of the nasal septum, suggested that arsenic might be capable of causing respiratory cancer It was, in consequence, often suggested that the small amounts of arsenic present in the ore were the agents responsible for the lung cancers observed among th miners of Jachymov and Schneeberg and among the nickel refiners of Sout Wales In fact, the evidence to implicate arsenic as a cause of lung cancer relatively slight. Four cases among sheep-dip workers were notified to th Ministry of Labour between 1939 and 1943 (Merewether 1944) and one occurre in a man making a sodium arsenite insecticide who had a heavily pigmente skin, numerous warts and a perforated nasal septum (Bridge 1940) *

The most important evidence derives from a study of causes of deat

* The 'case' which has sometimes been referred to as having been reported by Hopkins and Mc Studdiford (1934) appears to have been included erroneously as the patient concerned suffered fro cancer of the skin only

rates cited are crude rates and the sex and age distributions of the two groups must have differed greatly.

It would seem, therefore, that the evidence for the existence of a specific industrial hazard from exposure to iron dust or fumes, with or without additional exposure to silica, is suggestive, but that at the present time the case must be regarded as not proven.

Other Materials

Numerous other occupations have been thought to give rise to lung cancer (Hueper 1956, 1957*a*). Definite conclusions are not justified on the basis of the present evidence, but it would certainly be of interest to obtain further data for such industries as the manufacture of isopropanol, the mining and smelting of copper and the use of printing ink or of beryllium The manufacture of isopropanol appears to carry a risk of respiratory cancer, since 4 cases of the rare nasal cancer and 1 case of laryngeal cancer were observed among 71 employees who worked for more than 5 years in one plant (Weil, Smith and Nale 1952) Only one case of lung cancer among the employees has, however, yet been recorded A specific hazard from the handling of copper ore might be the explanation of the high mortality from lung cancer which has been observed in certain parts of Montana, where the mining and smelting of copper ores provide one of the principal sources of employment The data have been referred to previously (Table VI, p 47) in discussion of the risks possibly due to radioactivity The existence of a risk among typographers, exposed to printing ink, was suggested by Ask-Upmark (1955); he found that they constituted 8 out of 125 male patients with bronchial carcinoma who were aged over 40 years and resident in Stockholm, while he estimated that the proportion of men in similar occupations in Stockholm generally was less than 1 in 250. In this case the significance of the observations was enhanced by the finding that tumours could be produced experimentally by painting printing ink on the skin of mice.

The possibility that men exposed to beryllium might develop lung cancer was first suggested in 1948 because of the appearance of the sarcoid-like lesions in the lungs of beryllium workers and because the injection of beryllium intravenously was found to produce osteogenic sarcomas in rabbits (Gardner and Heslington 1946) Subsequently Vorwald (1955) found that bronchogenic carcinoma was produced in rats by exposing them over long periods to inhalation of beryllium dust The occurrence of lung cancer in a man with berylliosis has been reported by Kahlau (1954) and two other cases in men who had been exposed to beryllium were reported by Hardy (1955).

Two groups of occupations are of special interest. The first consists of those occupations in which the workers are heavily exposed to the dust from tarred roads and the exhaust fumes of motor vehicles If these agents are responsible for a substantial proportion of the general mortality from lung cancer, it would be expected that men who, by virtue of their occupation, are ·ily exposed to these agents would suffer an unduly high mortality from he disease. In fact, Kennaway and Kennaway (1947) found that during the

labourers' occupied fourth and fifth places in the list of occupations with a high mortality from lung cancer in the analysis of occupational mortality in England and Wales in 1930–32, with standardised death rates which were respectively 93 per cent and 88 per cent higher than average (Registrar General 1938) Data from Scotland for 1949–53 are similar (Registrar General for Scotland 1956; Morrison 1957). In two large scale studies of patients it has been found that a higher proportion of men with lung cancer than of men with other diseases could be described as 'hot metal' workers—the majority of whom are likely to have worked with iron (Wynder and Graham 1951; Breslow, Hoaglin, Rasmussen and Abrams 1954). A third study, however, failed to confirm this finding (Doll 1953*a*).

Evidence of a risk among haematite miners was obtained by Faulds and Stewart (1956). Haematite ore consists principally of ferric oxide but it also contains 10 to 12 per cent of silica. It has been mined in Cumberland since Roman times, but the introduction of new drills, just before the first world war, greatly increased the dustiness of the process and effective measures for the reduction of dust were not taken for over 20 years. The evidence consists, firstly, in the observation that the incidence of lung cancer at autopsy among the miners has increased sharply; from 4·4 per cent in 1932–47 (4 out of 91) it rose to 14·6 per cent in 1948–53 (13 out of 89). Secondly, the incidence has been greater than that found at autopsy among other Cumberland males aged over 30 years during the same period—*i.e.*, 9·4 per cent (17 out of 180) against 2·0 per cent (45 out of 2,221). Thirdly, the growths have been found on at least 6 occasions in close pathological association with sidero-silicotic masses and appear to have arisen from them.

These observations are, however, not conclusive. In particular, it is impossible to be sure that the incidence among the miners is really higher than normal. Autopsy data of this type are difficult to interpret because the subjects who come to autopsy may not be representative of the population from which they are drawn Even in the years since 1948 only 56 per cent of the miners who died came to autopsy These must be presumed to include the great majority of the miners dying with pulmonary symptoms, since compensation is payable if death is attributed to silicosis or to silico-tuberculosis If all the cases of lung cancer did, in fact, come to autopsy, the true incidence among the miners would have been 13 out of 160 or 8·1 per cent—a figure which is not very different from that which would have been expected from national mortality data among men of comparable ages. Among other Cumberland males, on the other hand, the reasons for which an autopsy is performed are presumably different—the most important is likely to be sudden death—and a lower proportion of cases coming to autopsy is likely to show lung cancer—even though the incidence of the disease in the whole population is similar to that among the miners

Other data on iron-ore miners were published by Hueper (1956) and these showed that the lung cancer of the miners in one Minnesota county was substantially higher than the death rate among Minnesota residents in general. It is, however, impossible to assess the significance of this difference as the

the additional fumes produced by the buses (to which the men in the bus garages would have been particularly exposed) were from petrol engines before 1937, but by 1951 they would have been wholly produced by diesel engines. In sum, therefore, the available occupational data do not suggest that exposure to road dust or motor fumes gives rise to a significant risk of the disease.

The second group of occupations consists of those which give rise to pneumoconiosis. For, if tissue injury is an important cause of cancer, it would be expected that these occupations might also give rise to a high incidence of cancer of the lung. In fact, most of the occupations in which a special risk of lung cancer has been established can also give rise to pneumoconiosis. The lung cancers which have occurred among asbestos workers have been almost uniformly associated with a severe form of pulmonary fibrosis. According to Hueper (1956) and Mancuso and Hueper (1951), chromitosis—a spotty fibrous thickening of the interstitial tissue—accompanies the development of lung cancer in chromate workers. In both these cases the pulmonary fibrosis occurs in direct association with the specific irritant. Some degree of interstitial fibrosis has been found in the lungs of nickel workers Løken (1950) regarded this as amounting to industrial pneumoconiosis in one case—in Jones Williams' experience (personal communication) the fibrosis present in five cases was more [illegible] ie degree of fibrosis [illegible] of those miners of [illegible] d on occasions the degree of silicosis was marked, lungs which were heavily affected were, however, usually free from cancer A similar disparity between the degree of fibrosis and the presence of cancer was noted in the lungs of haematite miners (Faulds and Stewart 1956), although, as has been stated previously, a substantial proportion of these cancers were regarded as arising directly from local siderosilicotic masses In contrast to these observations, however, silicosis occurs commonly in some occupations in which the risk of lung cancer is normal or low. Data collected by the Miners' Phthisis Medical Bureau (1936) in Witwatersrand showed that in over 3,000 necropsies on European miners the proportion in which lung cancer was found was the same, irrespective of the presence of silicosis—and both proportions were similar to that found at the Johannesburg General Hospital among men who had never worked underground Among South Wales coal-miners James (1955) found that, in each age group, lung cancer was less common at necropsy than among non-miners:

		Age			
		Under 50 years	*50–59 years*	*60–69 years*	*70 years and over*
Per cent lung cancer	Miners	2·3	3·8	3·7	2·7
	Non-miners	3·7	5·8	8·5	3·1

Among the miners, moreover, the incidence of lung cancer fell as the degree of pneumoconiosis increased:

	Simple pneumoconiosis			*Massive pneumoconiosis*
	Slight	*Moderate*	*Severe*	
Per cent lung cancer	5·9	4·0	4·1	1·4

period 1921–38 the mortality from lung cancer among such men was 47 per cent greater than the average observed throughout the country for men of the same ages. *More recent studies of the occupational histories of patients with* and without lung cancer have, however, failed to reveal any greater proportion of men who had been employed in such occupations among the lung cancer patients than among other patients with other diseases (Wynder and Graham 1951; Doll 1953*a*; Breslow *et al.* 1954). Doll's data are summarised in Table IX. The low proportion of policemen with lung cancer is striking, as many of them are directly exposed to the fumes of dense traffic for many hours daily.

TABLE IX

Past Occupational Histories of Special Exposure to Road Dust and Motor Fumes:

1,357 *men with lung cancer and* 1,357 *'matched controls'**

Occupation	*Number of men giving specified occupational history*	
	with lung cancer	*with other diseases*
Motor mechanics, garage hands	19	25
Drivers of cars, lorries, buses	105	101
Bus and tram conductors	10	21
Van drivers (horse)	33	25
Other road transport	17	25
Roadmen, council labourers, dustmen	39	39
Policemen	16	32

* Extracted from data published by Doll (1953*a*)

Observation of the incidence among men employed by the London Transport Executive has also failed to show any excess cancer morbidity which could be attributed to their occupation Raffle (1957) reported that among men aged 45 to 64 years, exposed to risk for a total of 92,345 years, 96 developed lung cancer, whereas 148 deaths would have been expected on the basis of the mortality rates for lung cancer recorded for all Greater London during a similar period It is difficult to understand why the mortality should have been relatively so low; but, even if some cases had failed to be recorded, there is no evident reason why the deficiency should have been greater in one group of workers than in another and the death rate among the men who would be more exposed to exhaust fumes (bus drivers and conductors, and engineering staff employed at the bus garages) was actually somewhat lower than among men who would be less exposed (drivers and guards on the underground railways and engineering staff at the trolley bus depots and at the repair shops), *i.e.*, 0·9 against 1·4 per 1,000 per year respectively. The fumes to which the men were exposed would have been largely those common to all users of the streets;

... the buses (to which the men in the bus ... engines before 1937, but by 19... ... engines. ... available occupational data do ... exposure ... risk of the disease ... se which give rise to pneumoconiosis For, if tissue injury ... use of cancer, it would ... expected that these occupations might also give rise to a high incidence ... of the occupations in which a special risk ... The ... almost ... to ... ous ... ing ... chromate workers

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		Age			
		Under 50 years	*50–59 years*	*60–69 years*	*70 years and over*
Per cent lung cancer	Miners	2·3	3·8	3·7	2·7
	Non-miners	3·7	5·8	8·5	3·1

Among the miners, moreover, the incidence of lung cancer fell as the degree of pneumoconiosis increased

	Simple pneumoconiosis			*Massive pneumoconiosis*
	Slight	*Moderate*	*Severe*	
Per cent lung cancer	5·9	4·0	4·1	1·4

CHAPTER VI

THE SMOKING OF TOBACCO

RICHARD DOLL

THE evidence linking tobacco with the production of lung cancer is derived from two principal sources. The great mass of evidence has been obtained from the retrospective study of patients with lung cancer and the comparison of their past smoking habits with the past habits of patients with other diseases, or with the habits of healthy persons. More recently, evidence of another type has been obtained by comparing, over a period of years, the mortality in groups of persons whose smoking habits had previously been defined.

RETROSPECTIVE STUDIES

The first serious study of the subject was reported by Muller in Germany in 1939. He obtained the smoking histories of 86 men with bronchial carcinoma from hospital notes, by personal interview or from a questionnaire sent to the relatives of those who had died and he compared the histories with those given by 86 healthy men of the same ages The results showed gross differences between the groups in the proportion of non-smokers and of heavy smokers. [illegible]

cancer than among patients with other diseases, and, with one exception (the difference between the proportions of non-smokers found by McConnell, Gordon and Jones 1952), the differences are large enough to merit serious attention More detailed results of two of the investigations are shown in Tables XI and XII From these it is seen (1) that there is a steady increase in the relative proportions of lung cancer to control patients as the amount smoked daily increases, and (2) that the difference in smoking habits holds for both sexes, but is more marked for men than for women

The method of smoking was not studied separately in all the investigations When it was the results agreed in showing that the difference between the lung cancer and the control groups was principally due to a difference in the proportion of cigarette smokers The results with regard to pipe smoking and cigar smoking were inconstant In some investigations it appeared that the disease was equally associated with all types of smoking (McConnell, Gordon and Jones 1952; Randig 1954), in the majority the disease was most closely associated with the smoking of cigarettes Few of the investigators made specific inquiries about inhaling. In one study it was found that the proportion of patients who said they inhaled was similar among the lung cancer patients

TABLE X

Principal Characteristics of the Smoking Histories of Men with and without Lung Cancer, Reported by Various Authors

Author	*Date*	*Country*	*Number of men*		*Percentage of 'non-smokers' among men*		*Percentage of 'heavy smokers' among men*	
			with lung cancer	*without lung cancer*	*with lung cancer*	*without lung cancer*	*with lung cancer*	*without lung cancer*
Müller	1939	Germany	86	86	3.5	16.3	65	36
Schairer and Schöniger	1943	Germany	93	270	3.2	15.9	52	27
Wassink	1948	Holland	134	100	4.5	19.0	55	19
Shrek *et al*	1950	U S A	82	522	14.6	23.9	18	9
Mills and Porter	1950	U S A	444	430	7.0	31.0	—	—
Levin *et al*	1950	U S A.	236	481	15.3	21.7	—	—
Wynder and Graham	1950	U S A	605	780	1.3	14.6	51	19
Doll and Hill	1950	Britain	649	649	0.3	4.2	26	13
McConnell *et al*	1952	Britain	93	186	5.4	6.5	35	22
Doll and Hill*	1952	Britain	708	708	0.7	4.8	24	14
Sadowsky *et al*	1953	U S A	477	615	3.8	13.2	—	—
Wynder and Cornfield	1953	U S A	63	133	4.1	20.6	68	29
Koulumies	1953	Finland	812	300	0.6	18.0	66	31
Lickint	1953	Germany	224	1,000	1.8	16.0	74	29
Breslow *et al*	1954	U S A	518	518	3.7	10.8	74	42
Watson and Conte	1954	U S A	265	277	1.9	9.7	73	57
Randig	1954	Germany	415	381	1.2	5.8	34	18
Gsell	1956	Switzerland	150	150	1.3	19.3	67	15
Kreyberg	1956	Norway	213	4,158	1.4	13.2	18	7
Schwartz and Denoix	1957	France	602	1,204	3.1	15.8	13	7

Note—It has not been possible to make all the figures completely comparable. Some series, for example, include a few women The individual papers should be referred to before any detailed use of the figures is made

* Doll and Hill's 1952 paper gave results for 1,357 men with lung cancer the results shown here relate only to those which were not included in the 1950 paper

PROSPECTIVE STUDIES

Confidence in this conclusion has been increased by the results of two prospective investigations, in which the smoking habits of large numbers of persons have been recorded and the frequency of occurrence of lung cancer among groups with different smoking habits has been observed. The investigations were carried out in Britain and the U.S.A. In the British inquiry (Doll and Hill 1954, 1956) a questionnaire was sent, at the end of October 1951, to all members of the medical profession in the U.K.; in addition to giving their name, address and age, they were asked to classify themselves into one of three groups, namely, (*i*) whether they were at that time smokers of tobacco, (*ii*) whether they had smoked and given up, or (*iii*) whether they had never smoked regularly. All smokers and ex-smokers were asked additional questions; smokers were asked at what age they had started smoking, the amount of tobacco they were smoking and the method of smoking at the time of replying to the questionnaire. The ex-smokers were asked similar questions relating to the time at which they had last given up smoking. Over 40,000 doctors replied and, from the information given, it was possible to classify them into broad groups according to their sex and age, the amount of tobacco smoked, the method of smoking and whether smoking had been continued or abandoned Subsequently, through the courtesy of the Registrars General, a form showing particulars of the cause of death was provided for every death identified as referring to a doctor, and information about additional deaths was provided by the General Medical Council and the British Medical Association. The results obtained are illustrated in Figures 10 and 11. In the 53 months covered by the study (November 1951 to March 1956) 1,714 deaths were recorded among male doctors aged 35 years and above who had previously provided details of their smoking habits, including 84 due to (or associated with) lung cancer. Of five disease groups studied, lung cancer was the only one for which there was a well marked and steady increase in mortality with the amount smoked. The actual death rate (standardised for age) rose from 0·07 per 1,000 in non-smokers (based upon the observation of only one death) to 0·47 per 1,000 among light smokers of 1–14 grammes a day* to 0·86 per 1,000 in moderate smokers of 15–24 per day and finally to 1·66 per 1,000 in smokers of 25 or more a day. That is, the death rate of heavy smokers was approximately 20 times the death rate of the non-smokers. It was found also that the mortality was substantially and significantly greater in cigarette smokers (1·25 per 1,000) than in pipe smokers (0·38 per 1,000) with the mortality for mixed smokers (0·68 per 1,000) falling in between, and these differences persisted when allowance was made for the fact that cigarette smokers tended to consume more tobacco than pipe smokers. The highest mortality was observed amongst those who were continuing to smoke at the time the questionnaire was completed (1·03 per 1,000). Among men who had given up smoking within 10 years previously the death rate was lower (0·59 per 1,000) and it was lower still amongst those who had given up for 10 or more years (0·35 per 1,000). Since the mortality

* 1 cigarette contains approximately 1 gramme of tobacco

from lung cancer was greater among cigarette smokers than pipe smokers and among present smokers than among past smokers, it is clear that the highest rates of mortality must have been recorded among those doctors who were continuing to smoke cigarettes at the time of the inquiry. In fact, mortalities among men in this group were substantially higher than the corresponding mortalities among all smokers which have been referred to previously. Thus for men aged 35 and over who, in November 1951, smoked 1–14 cigarettes

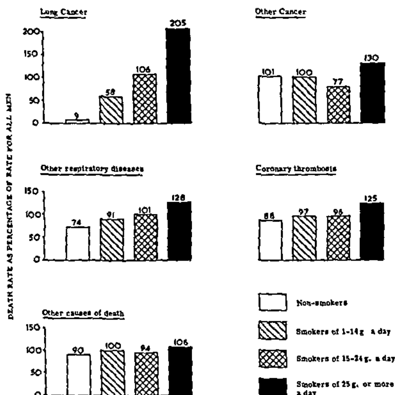


FIG 10

Mortality from 5 groups of diseases in relation to amount smoked death rates among men in 4 smoking categories expressed as a percentage of the rate for all men. (Doll and Hill 1956)

a day the subsequent annual mortality from lung cancer was 0 95 per 1,000, for those who smoked 15–24 a day 1·67 per 1,000 and for those who smoked 25 or more a day 2·75 per 1,000. In other words, the rates for the continuing cigarette smokers were 102, 67 and 66 per cent higher than the corresponding rates for all smokers past or present and in this group the rate among men who were smoking 25 or more cigarettes a day was almost 40 times the rate observed among non-smokers The relative levels of risk for the different amounts smoked are necessarily not very reliable, principally because only one death

from lung cancer was observed in a non-smoker. Errors, other than random ones due to the small numbers involved, must, however, have resulted in an understatement of the estimated differences. The reason for this is that the classification of smokers was based for the most part upon the smoking habits at one point in time; consequently, doctors will have been included in the light smoking group who had previously smoked heavily and for a long time, others will have been included as pipe smokers who had previously smoked cigarettes and some will have continued to be classed as smokers although they had subsequently given up. Thus the differences which would have been

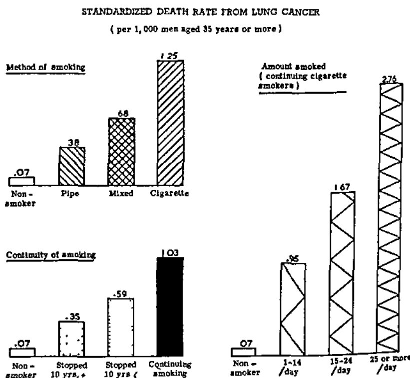


FIG 11

Mortality from lung cancer in relation to method, continuity and amount of smoking death rates per 100,000 men per year, standardized for age (After Doll and Hill 1956)

observed had a more exact classification been possible could only have been greater than those actually observed.

The results of the inquiry organised by the American Cancer Society have been similar (Hammond and Horn 1954, 1958). In this inquiry a large number of volunteer assistants each interviewed approximately 10 white men, aged between 50 and 69 years, chosen from among acquaintances with whom they expected to remain in contact for several years. The smoking histories obtained at the interviews were recorded on standard questionnaires and each year subsequently a follow-up form was completed stating whether the

The results of both these investigations, conclusive though they may appear, could be attributed to a bias inherent in the methodology of the investigations That they are unlikely to be due to bias is suggested by comparison of the results with those obtained by an entirely different method—that is, by retrospective study of patients' smoking habits. Such a comparison is shown in Figure 13. The quantitative relationships obtained between the amount smoked and the risk of the disease are practically identical and it is extremely difficult to believe that two such similar results could have been produced artificially as a result of the different types of bias which might theoretically have intruded into the two different methods of investigation. In fact, there appear to be only two ways in which the prospective inquiries could have been biased. Firstly, the diagnosis of lung cancer might have been made more readily if it were known that the patient was a heavy smoker than if he were known to be a light smoker or a non-smoker That this is not the explanation, however, is made almost certain by the finding that the relationship with smoking is stronger

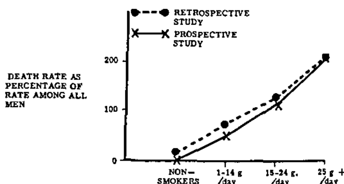


FIG 13

Mortality from lung cancer in relation to amount smoked results obtained by different methods of investigation.

for those patients in whom the diagnosis was established by biopsy or by autopsy than for those whom the diagnosis was made by less stringent methods (Doll and Hill 1956; Hammond and Horn 1958). Secondly, as Berkson (1955) has suggested, an initial bias might have been introduced by the selection, as subjects of the inquiry, of a group of persons with unrepresentative smoking habits. The effects of such selection must, however, wear off in the course of a few years, whereas the passage of time has, in fact, served to strengthen the results It must be concluded, therefore, that these prospective investigations, like the earlier retrospective ones, show the existence of a close relationship between the occurrence of lung cancer and smoking—particularly the smoking of cigarettes.

INTERPRETATION OF DATA

The evidence obtained by the retrospective studies of patients and the prospective studies on supposedly healthy individuals has established that there

is a relationship between cigarette smoking and the incidence of lung cancer. It does not, however, necessarily follow that smoking is a cause of the disease. Three explanations of the relationship are theoretically possible.

1. The effect of smoking might be to determine the site of appearance of a cancer, the occurrence of which—somewhere in the body—was predetermined by other factors. This concept is in line with a hypothesis put forward by Cramer (1934) that cancer susceptibility is determined by heredity and that the effect of environmental stimuli is to elicit the response in a particular tissue; hence the total incidence of cancer in a given population is supposed to be a fixed sum uninfluenced by changes in the stimulus—the primary site may change, the total incidence will not. In its general form the hypothesis is clearly untrue, since it has repeatedly been observed that a large excess of a particular type of cancer may be produced by exposure to a specific industrial hazard without lowering the risk of other types of cancer (Doll and Hill 1956). The hypothesis also fails to explain the present observations For it would require that types of cancer other than cancer of the lung should be *less* common among heavy smokers than among non-smokers and light smokers—and this is not true

2 An alternative explanation of the relationship is that some third and common factor both produces lung cancer and is also associated (directly or indirectly) with cigarette smoking It has, for example, been argued that since cigarette smoking is, in general, more prevalent in towns than in country districts, comparison of different smoking habits is, in fact, merely a comparison of urban and rural residents—and that the former are exposed to an atmospheric pollution which the latter escape This cannot be the explanation, however, since the relationship with smoking has repeatedly been shown to hold in both rural and urban areas independently (see, for example, Table XVII, p 85). Another suggestion has been that alcohol might be the primary factor, since heavy drinkers are also often heavy smokers. Wynder, Bross and Day (1956) have, however, shown that there is a close relation between lung cancer and smoking for a constant alcohol consumption, whereas there is no significant association with alcohol for a constant amount of smoking

Parnell (1951) and Fisher (1957*b*) have suggested that the risk of lung cancer may be determined by hereditary factors and that the same factors may determine the tendency to smoke cigarettes. Other possibilities may, perhaps, also be suggested, but in the absence of positive evidence in support it does not seem reasonable to attach much weight to them In fact, the relationship between smoking and the disease is so strong—the mortality increases about 40 times from that in non-smokers to that in heavy and persistent cigarette smokers—that it is extremely unlikely that it could be wholly explained by the existence of some third factor common to both. It is, of course, [illegible]

reason to abandon it now.

The results of both these investigations, conclusive though they may appear, could be attributed to a bias inherent in the methodology of the investigations. That they are unlikely to be due to bias is suggested by comparison of the results with those obtained by an entirely different method—that is, by retrospective study of patients' smoking habits. Such a comparison is shown in Figure 13. The quantitative relationships obtained between the amount smoked and the risk of the disease are practically identical and it is extremely difficult to believe that two such similar results could have been produced artificially as a result of the different types of bias which might theoretically have intruded into the two different methods of investigation. In fact, there appear to be only two ways in which the prospective inquiries could have been biased. Firstly, the diagnosis of lung cancer might have been made more readily if it were known that the patient was a heavy smoker than if he were known to be a light smoker or a non-smoker. That this is not the explanation, however, is made almost certain by the finding that the relationship with smoking is stronger

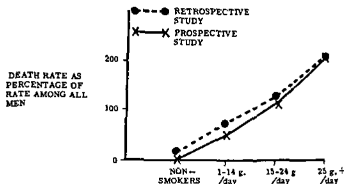


FIG 13

Mortality from lung cancer in relation to amount smoked, results obtained by different methods of investigation.

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3. The simplest explanation of the relationship is that cigarette smoking is a cause of the disease—that is of the principal histological types, other than adenocarcinoma. All the observations on cancer patients are consistent with this hypothesis, with the possible exception of the data on inhaling. Davies (1957) has, however, pointed out that in some circumstances deep inhalation must be expected to reduce the contact between the smoke droplets and the bronchial mucosa and, until more is known about the normal distribution of the smoke droplets in cigarette smoking, it is premature to attach any significance to these data. In the author's view, the explanation that cigarette smoking is a cause of lung cancer should be accepted unless it can be shown to conflict with any established facts which may be relevant to it.

National Statistics

Three of the principal facts referred to at the beginning of this Chapter were: (1) the increase in the death rate from the disease recorded over the past 50 years, (2) the great preponderance of male cases, and (3) the differences between the death rates recorded in different countries These observations have been related to corresponding changes or differences in cigarette consumption and the apparent agreement between the two sets of data has been cited as a reason for believing that tobacco is a cause of the disease. In fact, correlations of this type are often entirely irrelevant and they can certainly never prove the existence of a causal relationship. Nevertheless, if a relationship has been demonstrated by other means it is reasonable to inquire whether the national data for mortality and tobacco consumption are consistent with the idea that the one is a cause of the other.

The changes which have taken place in tobacco and cigarette consumption and in lung cancer mortality in England and Wales in the last 70 years are illustrated in Figure 14 and Table XIII. Whether the correlation between consumption and mortality is as close as would be expected if cigarettes were one of the principal causes of the disease is, however, uncertain, since the relevant facts are not all known. For example, it is not known:—

(1) What proportion of the increase in recorded mortality is real;
(2) what are the relative risks attached to the smoking of tobacco in cigarettes and other forms; or
(3) what is the biological relationship between the dose of cigarette smoke and the development of the disease.

More or less reasonable answers may, perhaps, be suggested, on the basis of present knowledge, for the first two questions, but the available facts are insufficient for any answer to be given to the third The evidence suggests that mortality varies in direct arithmetical proportion with the amount smoked at a given time, but there is little evidence about the normal length of the latent period and none at all about the relative effects of the same dose at different periods of life. Different hypotheses about either of these last characteristics would lead to gross differences in the estimates of mortality to

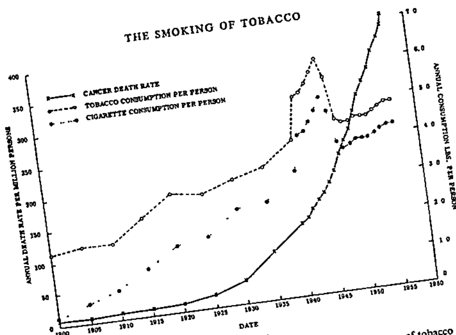


Fig 14

Trends in mortality from lung cancer in England and Wales and in consumption of tobacco and cigarettes in Great Britain, 1900–56

Table XIII

Tobacco Consumption and Lung Cancer Mortality in Britain, 1881–1955

Period	*Annual consumption lb per adult (15 years+)*			*Crude death rate from lung cancer per 1,000,000 adults (15 years+)*	
	Men		*Women*	*Men*	*Women*
	Cigarettes	*Other tobacco*	*Cigarettes*		
1881–1885	0 00	5 9	0 00		
1886–1890	0 05	5 9	0 00		
1891–1895	0 15	6 2	0 00		
1896–1900	0 6	6 1	0 00		
1901–1905	1 1	5 6	0·00		
1906–1910	2 2	4 5	0·00	22	13
1911–1915	3 0	4·0	0 00	21	11
1916–1920	4 5	4 5	0 00	34	15
1921–1925	4 7	4 1	0 12	57	21
1926–1930	5 6	3 5	0 3	126	39
1931–1935	6 2	2 9	0 6	212	55
1936–1940	7 7	2 5	1 1	312	67
1941–1945	9·0	2 6	2 3	516	97
1946–1950	7 9	2 3	2 3	802	125
1951–1955	7 8	2·0	2 6		

The figures for tobacco consumption are based on sales to the home population of the United Kingdom, the lung cancer death rates are crude rates for the total population of England and Wales

be expected from a given level of consumption. On some hypotheses, these estimates would not be very different from those actually recorded. It would, however, almost certainly be necessary to assume that the risk from pipe smoking was small in relation to the risk from cigarettes.

Whether differences in smoking habits can account for the preponderance of male cases and whether the changes in consumption which have occurred are consistent with the change in the sex ratio, are questions equally difficult to decide—and for the same reasons. From a knowledge of the distribution of smoking habits throughout the U.S.A., obtained by interviews with a randomly selected sample, Haenszel and Shimkin (1956) have calculated that the sex ratio attributable to differences in smoking habits would be expected to be about 3·6 to 1 in persons aged 35 years and above, whereas the observed ratio is about 5 to 1. To make this estimate they assumed that the risk of lung cancer increased in direct proportion to the duration of smoking If the risk actually rises at a greater rate than this (as is not unlikely) correspondence between the calculated and the observed ratios might well be still closer. Hueper (1954) asserts, on the other hand, that the increase in the sex ratio during a time when women have become responsible for an increasing proportion of the total amount smoked is evidence against the idea that cigarettes are a cause of the disease The problem is, however, not so simple. For example, Hueper fails to make any allowance for the effect of a long latent period following exposure before the disease appears In England and Wales the sex ratio, at all ages taken together, increased steadily from 1·7 to 1 in 1911–15 to 6·2 to 1 in 1951–55. When, however, the different age groups are considered separately it is seen that at ages 20–29 years the ratio has decreased from a maximum in 1926–30, at ages 30–39 years it has steadily decreased since 1936–40 and it is only at ages 50 years and above that the increase continues (see Tables I and II of Chapter I). The estimated consumption of cigarettes by women at different periods is shown in Table XIII and it is clear that there is not necessarily a conflict between the facts and the hypothesis, so long as it is assumed that there is a more or less long latent period after exposure before the appearance of the disease at the older ages.

If non-smokers alone are considered, the limited evidence now available is consistent with the view that in the absence of smoking (and exposure to the specific industrial carcinogens) the death rates for the disease are equal in the two sexes (Doll 1953*b*).

Attempts to compare mortality and tobacco consumption in different countries are even more hazardous Not only must all those factors, which have already been referred to, be taken into account, but it is also necessary to allow for possible differences in standards and fashions of diagnosis and for national differences in the method of smoking. Since, however, it has been asserted that national differences in mortality do not correspond at all well with differences in consumption, it is of interest to make the comparison—so long as its limitations are borne in mind. The result is shown in Figure 15 in which the crude male death rate from lung cancer in 12 countries in 1950 (or in the nearest year for which the information is available) is plotted against

the annual consumption of cigarettes per man; to allow for the effect of a long latent period, the cigarette consumption shown is that recorded for a period 20 years earlier. In 1930 nearly all cigarettes were smoked by men so that the rate of consumption per man has been assumed to be approximately double the rate per person. The countries included are all those for which data were obtained and which might be regarded as having approximately similar standards of medical service. From the Figure, it appears that the relationship between consumption and subsequent death rates is reasonably close, with the exception that the rate in Britain is too high and the rate in the U.S.A.

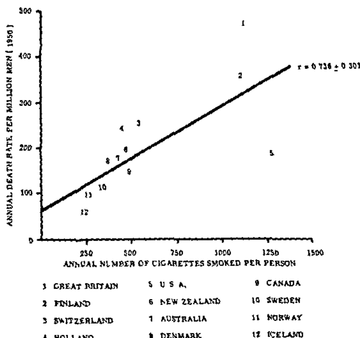


FIG 15

Lung cancer mortality and consumption of cigarettes in 12 countries in Australasia, North America and Western Europe lung cancer mortality in men in 1950 compared with the consumption of cigarettes per person in 1930

substantially too low. To a small extent the anomalous position of the United States can be explained by the high proportion of young people in its population. *A more important factor, however, may be that smokers in the U S.A throw* away a larger unsmoked butt than is commonly discarded in Europe; that this is so is the common opinion of many travellers and it is confirmed by such

It may be noted, however, that in the data from these two studies the ratio between the density of population in the most densely populated cities and that in the least populated rural regions was 350 to 1, while the ratio between the greatest and least mortalities from lung cancer was 3·5 to 1.

Evidence of a different type was obtained by Eastcott (1956) in a study of the lung cancer mortality in New Zealand. When the non-Maori population was divided into immigrants and those born in New Zealand and an allowance was made for the fact that immigrants were more likely to reside in the towns,

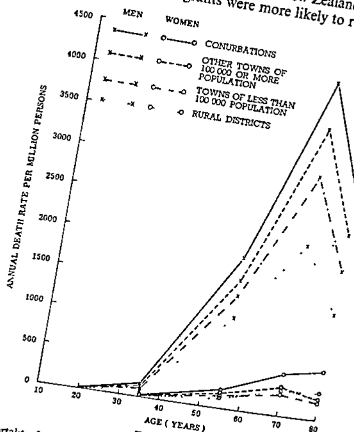


Fig. 16

Mortality from lung cancer in relation to degree of urbanisation: data for men and for women in four types of area in England and Wales in 1955.

it was found that the immigrants had a higher mortality from the disease and that the excess was particularly great among those who were aged 30 years or more at the time of immigration. Since both groups were predominantly of British stock it could be concluded that some factor in the British environment was responsible for the increased mortality among those who had immigrated into New Zealand. In Eastcott's view this factor was most likely to be atmospheric pollution associated with urbanisation.

There are, however, several anomalous findings which suggest that the

explanation of the urban-rural difference may not be altogether straightforward. Firstly, the difference between urban and rural mortality is most marked in countries with relatively little pollution. Secondly, the 'urban' factor seems to have affected the two sexes differently, whereas general atmospheric pollution might be expected to affect them almost equally. This effect is most evident in Norway. The data are illustrated in Figure 17, which shows that the recent increase in lung cancer mortality has principally affected men living in the towns; in consequence the urban-rural ratio in 1952–54 was 4 to 1 for men

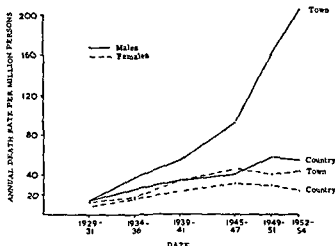


FIG 17

Trends in mortality from lung cancer in Norway, 1929–54 data shown separately for men and for women and for urban and rural areas (Pedersen, cited by Kreyberg 1956)

and only 2 to 1 for women (Pedersen 1956) The difference is less marked in Britain and Denmark, but the correlation which Curwen, Kennaway and Kennaway (1954) found between male mortality and density of population in the rural areas of Britain was absent for women (see Table XV) and in both countries there has been a greater predominance of male cases in the urban areas with a high mortality than in the rural areas with a low mortality

FACTORS OTHER THAN POLLUTION CONTRIBUTING TO THE DIFFERENCE

Three factors other than pollution may contribute to the excess urban mortality.

Firstly, the excess may be partly due to a greater efficiency of diagnosis in the areas of greater population density Bonser and Thomas (1955), for example, found that during 1950–52 the number of cases diagnosed in hospital in a largely rural region of Scotland was 21 per cent less than the number of persons recorded as having died of the disease, whereas in Leeds the deficiency was only 8 per cent; and Clemmesen, Nielsen and Jensen (1953) found a

similar difference in both sexes between the proportion of cases *not admitted* to hospital in the rural districts of Denmark and in Copenhagen. It is evident that access to hospital is less easy for patients in rural areas than in towns and it is reasonable to believe that some of the recorded differences may be spurious and due to differences in the extent to which the disease is recognised. Stocks and Campbell (1955) have, however, shown that this cannot be the whole explanation and their data suggest that it could hardly account for a deficiency in the rural areas of much more than 8 per cent of the urban mortality. This factor would not, of course, account for any part of the differences found by Eastcott (see p. 82)

Secondly, the excess may be in part due to occupational factors The number of men employed in occupations which are known to carry specific risks of the disease is small and unless new risks are discovered among men employed in common occupations, this factor cannot be of major importance. It may, however, contribute to the higher sex ratio found in some of the urban areas.

Thirdly, the urban-rural difference may arise partly from differences in the way of life of individuals in town and country. Indeed Kreyberg (1954) came to the conclusion, from a study of a large group of patients in Norway, that such differences might account for the whole urban excess, since he was unable to correlate the incidence of the disease with the degree of pollution as indicated by the industrialisation of a town or by the extent to which it was sheltered from the sea winds. One specific difference which needs to be taken into account is a difference in smoking habits. With one exception—in which the data were all collected from a single occupational group (Doll and Hill 1956) —all investigations have shown that townsmen both smoke more and consume what they smoke more often in the form of cigarettes than do countrymen Similar findings in this respect have been reported from Denmark (Hamtoft and Lindhardt 1955, 1956), England (Doll and Hill 1952; Stocks and Campbell 1955), Norway (Kreyberg 1955) and the U.S.A. (Haenszel, Shimkin and Miller 1956). The principal data for Denmark are summarised in Table XVI. In view of the substantial differences in mortality which have been

TABLE XVI

*Smoking Habits of Men in Different Areas of Denmark in 1952–53**

Part of Denmark	*Percentage of*				
	Non-smokers and ex-smokers	*Light cigarette smokers*	*Moderate and heavy cigarette smokers*	*Pipe smokers*	*Smokers of cigars and cigarettes*
Copenhagen	18 5	23 7	12 7	28 9	16 2
Provincial towns	20 9	18 1	7 2	37 4	16 4
Rural districts	25 8	10 5	2 4	45 3	15 9

* Extracted from data given by Hamtoft and Lindhardt (1956)

recorded between heavys mokers and non-smokers and between cigarette smokers and pipe smokers, it is clearly essential to allow for these differences in smoking habits before any difference in mortality can be attributed to an independent effect of urbanisation. Had Eastcott (1956), for example, contrasted the cigarette consumption of Britain and New Zealand, rather than the total tobacco consumption of the two countries, he would have found that the extent of the difference was not very dissimilar from that observed between the mortalities of native born New Zealanders and British immigrants (see p. 82) *

THE CONTRIBUTION OF ATMOSPHERIC POLLUTION

Attempts to distinguish quantitatively between the effects of smoking and the effect of urbanisation have been made by four groups of investigators Haenszel and Shimkin (1956) used the results of a nation-wide survey of smoking habits undertaken by the U S. Bureau of the Census (Haenszel, Shimkin and Miller 1956) and the various estimates which had been made of the relative risks associated with different levels of smoking On this basis, they calculated that differences in smoking habits would account for an urban excess among men of only 13 per cent, whereas the recorded excess was 85 per cent: among women the agreement was somewhat better—the calculated excess was 15 per cent and the recorded excess 31 per cent

Perhaps the clearest evidence has been obtained by Hammond and Horn (1957) in their prospective study of supposedly healthy individuals This study was on such a large scale that a direct comparison of the mortality among cigarette smokers and non-smokers could be made for four types of area differing in the degree of urbanisation. From Table XVII it is seen that the mortality observed among men resident in the largest towns was 58 per cent

TABLE XVII

Mortality from Lung Cancer in Town and Country in the U S A. in Men Aged 50–69†

Type of case	*Rates standardised for*	*Death rate per 100,000 men per year in*			
		Cities of 50,000 population or more	*Cities of 10,000–50,000 population*	*Suburb or town*	*Rural*
All certified cases	Age	82	68	73	52
	Age and smoking habits	75	66	73	59
Well established diagnosis, excluding adenocarcinoma of lung	Age	56	46	43	34
	Age and smoking habits	52	44	43	39

* This may, however, be an over-simplification as much of the tobacco in New Zealand may have been smoked in the form of hand-rolled cigarettes and this has not been allowed for

† After Hammond and Horn (1957).

higher than that observed among men resident in rural areas, but when differences in the amount smoked were taken into account the excess mortality was reduced to 27 per cent, *i.e.*, by about half. The death rates actually observed among cigarette smokers and among men who had never smoked regularly are shown in Figure 18 In both sets of data, the rates are higher in the large towns than in the country with the rates for smaller towns and suburban areas intermediate.

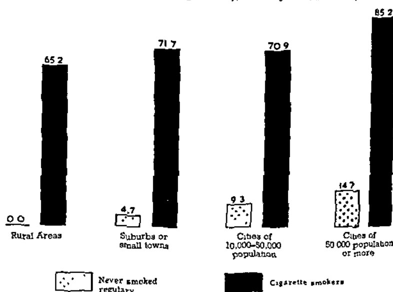


FIG 18

Mortality from lung cancer in the U.S A in relation to degree of urbanisation and smoking habits. death rates standardized for age. only cases with well established diagnosis included and adenocarcinomas excluded (After Hammond and Horn 1957)

Other data have been obtained by Stocks and Campbell (1955) and by Doll and Hill (unpublished) In these studies the smoking habits of the general population were estimated from the habits recorded, at a personal interview, by hospital patients suffering from diseases other than lung cancer and the habits of persons dying of lung cancer were determined similarly by interview with hospital patients suffering from the disease or, in the case of some of the patients in Stocks and Campbell's study, by interview with a close relative after death. The results of the two studies are illustrated in Figure 19. In both cases the male mortality was found to be higher at each level of smoking in the larger towns (Liverpool and Greater London respectively) than in the rural districts. The only major discrepancy concerns the mortality rates among non-smokers: according to Stocks and Campbell's data this varied appreciably

with the degree of urbanisation, while according to Doll and Hill's data the variation was slight Stocks and Campbell stress the fact that the ratio of the rural to the Liverpool rates increases steadily with the amount smoked and they regard the data as suggesting that the Liverpool environment exposes men to a carcinogen which adds to the rural rate a certain fixed risk of lung cancer (equivalent to about 100 deaths per 100,000 men aged 45 to 74 years per annum) irrespective of whether they smoke or not They summarise their

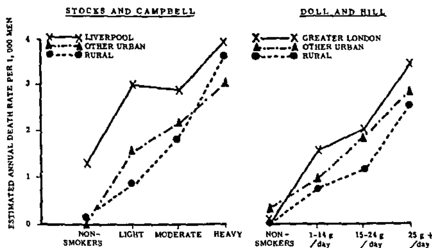


Fig 19

Mortality from lung cancer in relation to degree of urbanisation and amount smoked death rates estimated from data obtained in retrospective studies of patients' smoking habits (Stocks and Campbell 1955, Doll and Hill, unpublished data)

results by estimating that if all the men in Liverpool had been non-smokers the number of deaths from lung cancer would have been reduced by about 53 per cent and if the specific local cause were removed the death rate would be reduced by a further 36 per cent It may be noted, however, that if the same technique were applied to their data for the mixed urban and rural areas of Cheshire, the conclusion would be reached that local factors were not responsible for any of the deaths

In the author's view, the comparisons made of the mortality among smokers in different areas are liable to overestimate the difference between the areas For if, as seems probable, the habit of cigarette smoking spread from the towns into the countryside, it must be expected that differences in smoking habits 20 to 30 years ago—the more relevant period for the induction of cancer—would have been greater than they are now, and comparison based on the most recent habits will underestimate the differences in habits between the various areas and so will overestimate the difference in mortality due to other factors. It is doubtful whether this could be overcome by basing the comparisons on the histories of the more remote habits, since the histories of habits in the distant past are much less reliable. This defect does not apply to the data

obtained on non-smokers and these data may, therefore, give a better estimate of the effect of the 'urban' factor than the data on smokers. Such data are, however, extremely difficult to collect owing to the small numbers of cases recorded among non-smokers.

In an attempt to overcome this difficulty, Doll (1953*b*) grouped together male and female cases occuring in non-smokers and, on the basis of the data collected by Doll and Hill (1952), estimated that the difference in mortality attributable to local factors might be insignificant. He was unable to find any evidence for a difference in mortality among non-smokers in the two sexes, but, if there should be a difference, the procedure would clearly not be justified. The estimates of the rates in non-smokers obtained in the 3 investigations are summarised in Table XVIII.

TABLE XVIII

Death Rates from Lung Cancer among Non-smokers in Areas of different Degrees of Urbanisation

Age and sex of population	*Number of deaths among non-smokers*	*Estimated death rate per 100,000 persons per year in*			*Reference*
		rural districts	*areas of intermediate urbanisation*	*large towns*	
M 50–69 years	10	3	11	26 (*a*)	Hammond (1956)*
M 45–74 years	25	14	0	131 (*b*)	Stocks and Campbell (1955)
M 45–74 years	4	0	26	11 (*c*)	Doll and Hill (1952)
M and F 45–74 years	40	13	11	14 (*c*)	Doll (1953*b*)

(*a*) Pittsburg, Los Angeles, Chicago, Detroit, Buffalo, Syracuse, Minneapolis and Newark
(*b*) Liverpool
(*c*) Greater London

* The later data published by Hammond and Horn (1958) are not comparable with the other data in this Table, since they relate only to histologically proved cases, and exclude adenocarcinomas

At the present moment it is not possible to reach a definite conclusion about the extent to which atmospheric pollution is responsible for the production of the disease. The most extreme estimate, based on Stocks and Campbell's data, is that in certain towns with heavy pollution (like Liverpool), the local 'urban' factor may be responsible for approximately two-fifths of the cases. In view, however, of the low rate observed among non-smokers in Doll and Hill's prospective study on British doctors—7 per 100,000 male non-smokers aged 35 years and above against 81 per 100,000 for all men of the same age groups—it is difficult to believe that the factor can make such a large contribution to the national rate for men throughout the country as a whole. In fact, more conservative estimates, based on all the British data, would suggest that in many urban areas (including perhaps Greater London) the effect of the 'urban' factor may be very small or even absent. In the U.S.A. it appears from

Hammond and Horn's data that local 'urban' factors may be responsible for approximately a quarter of the cases in the big towns and about one-eighth in the smaller towns and suburban areas.*

The belief that some cases of lung cancer are attributable to an 'urban' factor is strengthened by the knowledge that the air of towns is polluted by the presence of several known carcinogens, and that, within a single country, the concentration of these substances tends to be greater in the larger towns. Four groups of substances have been recognised: arsenic, radioactive elements, 3:4-benzpyrene and other polycyclic hydrocarbons and, possibly, the oxidation products of aliphatic hydrocarbons. The amounts of arsenic and benzpyrene which have been found in urban air are shown in Table XIX. In Britain,

TABLE XIX

Average Annual Amount of Smoke, 3:4-Benzpyrene and Arsenic in the Air of British and Scandinavian Towns†

Place	*Smoke* $mg/100m^3$	*3:4-benzpyrene* $\mu g/100m^3$	*Arsenic* (As_2O_3) $\mu g/100m^3$
London (Beckton)	29·2	7·1	13·2
" (County Hall)	29·5	4·6	5·8
" (Crossness)	—	1·6	—
Liverpool	36·3[1]	7·7[1]	—
Sheffield	39·3	4·2	6·5
Bristol	6·7	1·3	3·7
Hull	30·0	1·8	5·4
Leicester	14·1	2·9	—
Burnley	30·3	2·7	—
Cannock	7·3	1·9	—
Bilston	30·0	2·7	7·5
Llangefni (Anglesey)	4·9[1]	0·7[1]	—
Copenhagen	5·1	1·0	1·8[1]
Oslo	2·2	0·6	1·8
Bergen	6·0[1]	1·2[1]	—
Notodden (Norway)	0·8	0·3	—
Reykjavik	1·3	0·25[2]	0·1
Akureyri (Iceland)	0·6	0·05[2]	—

[1] Winter average [2] Summer average

† Extracted from data published by Campbell and Clemmesen (1956), Campbell and Kreyberg (1956), Goulden, Kennaway and Kennaway (1952), Kennaway (1957), Stocks and Campbell (1956) and Waller (1952) with additional data given by Dr J M Campbell and Sir Ernest Kennaway

both the arsenic and the polycyclic hydrocarbons are derived principally from coal smoke; in Los Angeles, on the other hand, Kotin and his colleagues believed that the presence of benzpyrene could be attributed almost entirely to the exhaust products of internal combustion engines (Kotin, Falk, Mader and Thomas 1954).

The mean amount of arsenic (As_2O_3) in the air of a large British town is of the order of 7 $\mu g/100m^3$ (Goulden, Kennaway and Urquhart 1952). A 'standard' man may be assumed to inspire about 7,300m^3 of air a year, so that

* See footnote to Table XVIII

the amount of arsenic inspired in the course of 10 years would be about 5 mg; this is little more than would be volatilised in smoking one cigarette a week over the same period and is equivalent to one maximum official dose of Fowler's solution. It is unlikely, therefore, that the presence of this small amount of arsenic could be of any serious significance.

The position with regard to the polycyclic hydrocarbons is different The most important of these is 3 : 4-benzpyrene, but others believed to be carcinogenic (*e g.*, 1:12-benzperylene) are also present in town air. The mean concentration of the benzpyrene in the air varies from town to town, but a representative value for a large British town is of the order 3 $\mu g/100m^3$. The amount inspired by a standard man in the course of 10 years would be, therefore, about 2 mg.; this is about equal to the amount inspired by a man smoking 50 cigarettes a day over the same period and is of the order of 500 times the dose which has produced a sarcoma when injected subcutaneously in a mouse. It is probable, however, that the amount which actually reaches the bronchi is appreciably less. Firstly, all measurements have been made on outside air and some of the suspended matter is likely to be filtered off before it is respired in, for example, bedrooms. Secondly, air is normally respired through the nose and more will be filtered off by the turbinates. Stocks and Campbell (1955) made the empirical assumption that about one-twelfth reaches the bronchi and consequently were able to show that in a rural area of North Wales, a mixed urban and rural area in Cheshire and Denbighshire and the town of Liverpool, the mortality rates from lung cancer might be closely proportional to the sum of the amounts of benzpyrene reaching the bronchi from the suspended matter in air and from cigarette smoke. It would, therefore, seem reasonable to postulate as a working hypothesis, that the benzpyrene derived from these two sources is the agent responsible for the production of the great majority of cases of the disease. The hypothesis would not be seriously affected if it should prove, as some other data suggest, that the mortality rates for non-smokers in the large towns were appreciably less than the rates estimated by Stocks and Campbell (1955) for Liverpool; in this case, it would merely be necessary to assume that less than one-twelfth of the suspended matter in town air reached the bronchi If, however, the benzpyrene in town smoke is wholly adsorbed on to carbon particles, it may be biologically inactive Steiner (1954) found that he could produce cancer of the skin of mice by means of extracts of smoke particles, but not by application of the untreated smoke itself, and this finding weighs against the hypothesis that atmospheric benzpyrene is a cause of the disease. On the other hand, Kotin, Falk, Mader and Thomas (1954) suggest that the aliphatic hydrocarbons and their oxidation products in the exhaust fumes of motors might act as eluents in the atmosphere and so reactivate the benzpyrene.

The radioactivity in air is small in amount and is unlikely to be a cause of more than a small proportion of the total number of cases—if, indeed, it is a cause of any. It is possible, however, that it might contribute to a somewhat greater number in the towns than in the countryside. The evidence is reviewed in a later section (p. 95).

The fourth group of substances which need to be considered are the oxidative products of aliphatic hydrocarbons Interest in these substances was aroused when Kotin and his colleagues reported that they had obtained tumours on the skin of mice by the application of an extract of substances obtained from atmospheric aerosols, which was free of polycyclic hydrocarbons (Kotin and Falk 1955; Kotin, Falk and Thomas 1956). The first tumour appeared after 14 months and altogether 5 out of 35 mice developed papillomas and 2 others developed cancers. The production of an increased number of pulmonary adenomas in mice exposed to atmospheres containing the aerosols was also demonstrated by Kotin and Falk (1956). The material was obtained synthetically by volatilizing gasoline with nitrogen and reacting it with ozone and is presumed to be similar to material occurring in urban atmospheres as the result of pollution by vehicular exhausts. It is suggested that the repsonsible agents might be epoxides or hydro-peroxides, some of which have been shown to have carcinogenic properties (Hendry, Homer, Rose and Walpole 1951, Fieser, Greene, Bischoff, Lopez and Rupp 1955). The work is, however, at too early a stage for any definite conclusions to be reached about the possible effect of this group of substances, under the conditions of normal town life

Effect of Fumes from Internal Combustion Engines

In recent years interest has been aroused in the extent to which the fumes from internal combustion engines can have contributed to the various effects of atmospheric pollution They are of particular interest in relation to lung cancer for two reasons Firstly they constitute a relatively new source of pollution which began to become prevalent some years before the rise in lung cancer mortality began to be recorded It should be noted, however, that this applies only in the case of the fumes from petrol-driven engines; diesel engines did not come into general use on the roads in Britain till after the rise in lung cancer mortality had commenced (Table XX) and a latent period of 20 or more years would normally be expected before the appearance

Table XX

Number of Diesel-engined Vehicles Registered for use on the Roads compared with the Male Death Rate from Lung Cancer

Year	*Number of diesel-engined vehicles registered in Britain*	*Per cent of total vehicles registered*	*Crude death rate from lung cancer per 1,000,000 men*
1910	0	0·0	12
1920	0	0 0	17
1925	0	0 0	27
1930	1	0 0	55
1934	6,715	0 3	108
1938	25,943	0 8	172
1942	—	—	223
1946	45,942	1 5	324
1950	88,597	2 0	480
1954	139 430	2 4	651

of any cases of lung cancer which might be attributable to their use. Secondly, the fumes of both types of engine have been shown to be capable of containing carcinogenic substances under certain conditions of operation. The data shown in Tables XXI and XXII are summarised from reports by Kotin, Falk and

TABLE XXI

*Pollutants in the Exhaust Gases from a Petrol Engine, under Different Conditions of Operation**

Revolutions per minute	*Load*	*Amount in 1 minute samples (μg)*	
		Pyrene	*3 : 4-benzpyrene*
500	0	225	120
1,000	0	439	61
1,500	0	507	33
2,000	0	374	40
2,500	0	346	25
3,000	0	121	13
3,500	0	48	10
1,000	1/4	59	0
2,500	1/4	7	0
1,000	2/4	26	1
2,500	2/4	11	0
1,000	4/4	21	0
2,500	4/4	0	0

* Extracted from data given by Kotin, Falk and Thomas (1954)

TABLE XXII

*Pollutants in the Exhaust Gases from a Diesel Engine, under Different Conditions of Operation**

Method of operation	*Revolutions per minute*	*Load*	*Amount in 1 minute samples (μg)*	
			Pyrene	*3 : 4-benzpyrene*
Efficient	1,200	0	9	0
	1,200	1/4	15	0
	1,200	2/4	16	0
	1,200	3/4	8	0
	Acceleration and deceleration	0	15	0
	,,	1/4	0	0
	,,	2/4	0 5	0
	,,	3/4	0 2	0
Inefficient	1,000	0	137	146
	1,200	0	208	9
	1,400	0	188	80
	1,000	2/4	536	772
	1,200	2/4	448	437
	1 400	2/4	220	1,372
	1,000	4/4	2,500	876
	1,200	4/4	1,912	1,706
	1,400	4/4	822	1,687

* Extracted from data given by Kotin, Falk and Thomas (1955).

Thomas (1954, 1955); they show that the conditions under which the maximum amounts of polycyclic hydrocarbons are produced differ markedly in the two types of engine With the petrol engine the maximum amounts of pyrene and of benzpyrene are produced when the engine is idling under zero load; increase of load or speed both result in a sharp reduction With the diesel engine, on the other hand, the amounts produced vary very slightly with speed but, under conditions of inefficient operation, increase sharply with load Under conditions of efficient operation very little of any of the polycyclic hydrocarbons is produced, irrespective of load and of whether the engine is running at a constant speed or accelerating and decelerating, under these conditions no benzpyrene was detected in the exhaust gases on any occasion Commins, Waller and Lawther's (1956) data support this conclusion. They made measurements simultaneously inside and outside a large London Transport Executive diesel bus garage while 200 buses were being brought in or warmed up before departure On a night when 'normal' urban pollution was high the benzpyrene content of the air inside and outside were virtually the same, although the soot content of the air inside was appreciably higher. On another night when there was little smoke in the outside air, a small amount of benzpyrene may have been added in the garage but the difference was so small that it could not be established with certainty and was negligible in comparison with the fluctuations which arise from varying levels of smoke outside.

In addition to the polycyclic hydrocarbons Kotin and Falk believe that various oxidation products of the aliphatic hydrocarbons may be present in the exhausts and that these may also be carcinogenic (see p. 91), while petrol vapours and their oxidation products might be capable of exerting a further effect by eluting the benzpyrene already in the air from other sources and thus potentiating its biological activity

Direct evidence of the effect of motor exhausts on persons specifically exposed to them is difficult to obtain All city residents are exposed to some extent in their daily life and it may be questioned whether any one group is exposed to any substantially greater degree In so far as there is such a group, it is likely to include men whose work keeps them on the roads or in garages

therefore, it is not possible to reach any definite conclusion about the effect of motor exhaust fumes There is no direct evidence to show that they give rise to any cases of lung cancer in man, but from the chemical evidence it may be presumed that they produce a proportion of those cases which can be attributed to atmospheric pollution in general; in Britain the proportion may well be small There is no reason to suppose that diesel engines have been more dangerous, in this respect, than petrol engines; operated efficiently they may be presumed to be safer. There are, however, no quantitative data which would allow a direct comparison to be made of the exhaust fumes of the two types of engine run under average conditions of operation

CONCLUSION

The data connecting atmospheric pollution with the production of lung cancer are not easy to interpret. The consistent finding of an increased mortality in large towns and the isolation from the urban atmosphere of *substances which are known to be carcinogenic to animals under suitable* experimental conditions, provide reasonable grounds for adopting, as a working hypothesis, the view that pollution is responsible for a proportion of cases. The carcinogenic substances in the atmosphere may, however, not be in a biologically active state and it certainly cannot be assumed that they are carcinogenic to the human bronchi simply because, under different conditions, they can produce cancer in other animals. Before the hypothesis is established it is necessary to relate pollution directly to the occurrence of the disease in man. Occupational studies of men heavily exposed to pollution have so far failed to provide such evidence and comparisons of urban and rural mortality are complicated by the existence of differences which characterise urban and rural life, other than in the degree of pollution of the atmosphere. The most important of these is the difference in the amount of cigarette smoking. Estimates of the mortality in different areas at different levels of smoking are in general agreement in showing that the mortality is higher at each level in the most densely populated regions, but they conflict in one important respect, namely, the extent of the mortality among non-smokers.

On present evidence it seems probable that atmospheric pollution is responsible for a proportion of cases The size of the proportion will be different in different countries; in Norway it is likely to be negligible, but even in Britain, where pollution is heavy, the proportion is unlikely to be large.

CHAPTER VIII

OTHER FACTORS: NON-INDUSTRIAL RADIOACTIVITY, RESPIRATORY INFECTION AND HEREDITY

RICHARD DOLL

NON-INDUSTRIAL RADIOACTIVITY

THE presence of radioactivity in the air is due primarily to the release of radon and, to a less extent, of thoron by the decay of elements in the ubiquitous uranium and thorium series In addition small amounts of radon and radium are ejected into the atmosphere by the combustion of coal and a very small amount is due to the presence of other radioactive elements (e g, radioactive carbon) *

The average radioactivity of the atmosphere was estimated by Dawson (1952) to be of the order of 5×10^{-14} curies/litre and this agreed fairly well with estimates made earlier in the century in England, Canada and the U S A (2×10^{-14} to 2×10^{-13} curies/litre) Dawson's estimates were, however, made by drawing air through filter papers and deducing the radon content of the air sample by assuming that the radon was in equilibrium with the radium A, B and C on the retained particles. Anderson, Mayneord and Turner (1954), however, pointed out that the method would underestimate the amount when the suspended particles were very small and they obtained values 10 to 100 times greater than with the filter paper method by measuring whole air samples in an ion-chamber apparatus. With this apparatus, they found that the average value for air on the roof of the Institute of Cancer Research, London, was 2 to 3×10^{-12} curies/litre

There are, however, large fluctuations in activity which are chiefly related to meteorological conditions During conditions of fog, both coal smoke and the radon naturally diffusing from buildings and the soil are likely to be retained near the surface of the earth and a considerable increase in radio-activity may be observed On the first day of the London smog of December 1952, Anderson, Mayneord and Turner (1954) found a level 400 times that recorded on a clear and sunny day The data on which Anderson, Mayneord and Turner's figure for the average radioactivity was based appear to have been collected under somewhat atypical meteorological conditions and further observations over a longer period now suggest that a lower figure—*i.e*, 2×10^{-13} curies/litre—would be more representative (Turner, personal communication) This figure is, however, representative only for the air outside a particular building. The activity indoors is not necessarily the same as that out of doors

* The small amounts of radioactivity attributable to other substances are not distinguished from that attributable to radon in the remainder of this section

diagnostic radiography. If small doses should prove to be capable of causing cancer, the contribution of this latter source (and of other quantitatively even less important sources) would also have to be considered. If any tumours, other than those due to specific industrial hazards, are due to radioactivity, it must be presumed that they would be similar histologically to the Jachymov and Schneeberg tumours—that is, they would almost invariably be squamous, oat-cell or undifferentiated cancers.

Respiratory Infection

Previous inflammation and the formation of scar tissue in the lungs have long been thought to be possible precursors of lung cancer. In support of this belief, it was pointed out that metaplasia and disorganised proliferation of the basal cell layer of the bronchial mucosa might follow from severe respiratory infection (Haythorne 1912; Goldzieher 1918) and, as has been clearly demonstrated by Auerbach and his colleagues (*1955, 1957*), similar changes are found more commonly in association with death from lung cancer than with death from other causes (see Table XIV).

In some cases of fatal influenza the histological picture in the bronchi so closely resembled that of early carcinoma that Winternitz, Wason and McNamara (*1920*), Shaw (*1924*) and others were led to predict that the *1918–19* pandemic of influenza would be followed by an increase in the incidence of lung cancer In fact, the increase in incidence has occurred, but it is most unlikely to be due to the epidemic of influenza. Firstly, the increase has affected men much more than women, whereas influenza affected both sexes almost equally. Secondly, the distribution of the increase throughout the world has not corresponded with the distribution of influenza; the epidemic was particularly severe in Iceland but Iceland has, until very recently, not suffered an increase in lung cancer Thirdly, the increase has affected persons who were not born at the time of the influenza pandemic; in England and Wales, for example, the lung cancer mortality among men aged 30 to 34 was 6 per million in 1916–20 and 35 per million in 1951–55.

Other pathological evidence derives from the observation that pulmonary tumours have been found in proximity to the scars of other pulmonary lesions Woodruff and Nahas (1951) and Woodruff *et al* (1952) found that calcified foci were present in the same lobe as the tumour or in the tracheo-bronchial nodes draining the lobe, in 27 out of 40 cases of squamous and anaplastic bronchial cancer—and that these foci were larger than those present in any other part of the lung; in contrast, there was a similar focus in only one out of [illegible] They suggested that calcified foci might [illegible] cinogenic [illegible] following primary tuberculosis might be a factor. A similar type of conclusion was suggested by Schwartz (1950), who described cases of bronchial carcinoma in association with lesions of the bronchial wall brought about by neighbouring tuberculous lymph nodes

An intimate histological association between cancer and scarring in the lung was described by Rössle (1943), Raeburn and Spencer (1953), and Lüders and Themel (1954) Raeburn and Spencer sectioned the whole of both lungs at autopsy and removed all suspicious nodules and scars for microscopy, irrespective of the cause of death In 750 autopsies, they found 9 unsuspected microscopic cancers in association with scars in the periphery of the lung and one unsuspected small carcinoma in a large bronchus. Difficulty was experienced 'in determining the borderline between innocent reparative proliferation and true malignant change', but the authors were satisfied that 'only cases which have shown obvious malignant change have been included in the series'. If the lesions were, in fact, true cancers, it must be postulated that their evolution into clinical malignancy would have taken many years, since otherwise their incidence was much greater than could be explained by the known rate of cancer mortality. Some doubt about the clinical significance of these lesions is, however, raised by the fact that four out of the nine 'cancers' occurred in women. Lüders and Themel examined 74 cases of lung cancer coming to autopsy at one Berlin hospital during the period 1949–53 and found evidence that the growth arose peripherally in 26. In 21 it appeared to be connected with a pulmonary scar During the same period 3 other 'scar cancers' were seen in material examined at other hospitals Of these 24 cancers, 4 were related to scars of primary tuberculous infections and 17 to scars of reinfections (10 apical, 6 infraclavicular and 1 elsewhere). In the remaining 3 cases the scars were classified as the result of pulmonary infarcts Rössle (1943) and Raeburn (1956) have drawn attention to the fact that pulmonary scars may be rich in cholesterol and, in view of Hieger's (1949) finding that pure cholesterol is a weak carcinogen, this offers a possible explanation of the method by which the growths are produced

The finding of lung cancer in association with certain types of pneumoconiosis has been described in a previous section (p 57) With some types of pneumoconiosis, not necessarily gross (*e.g* , chromitosis), the incidence of lung cancer is high; with other types, which may be very gross (*e g* , silicosis), the incidence may be normal or low In these industrial cases, it is clear that the disease is not the result of non-specific scarring, but results from the presence of a specific agent, which may or may not require the production of pulmonary fibrosis as an ancillary co-factor.

Several groups of investigators have studied the possible effect of previous respiratory infections by inquiring into the past medical histories of lung cancer patients Bryson and Spencer (1951), for example, found that a history of a long-standing bronchitis was recorded in 21 per cent of 866 cases In three reports the past histories have been compared with those obtained from 'control' patients with other diseases. Doll and Hill (1952) obtained histories from 1,465 patients with lung cancer and compared them with the histories given by 853 patients with cancer in other sites After making allowance for differences in the age and sex distribution of the patients, they found that the proportions admitting to respiratory tuberculosis, pleural effusion, asthma or chronic nasal catarrh more than five years previously were practically the same

in both groups, but that the proportions admitting to chronic bronchitis or pneumonia more than five years previously were significantly greater in the groups with cancer of the lung. When, however, these patients were compared with another group of 335 patients who had been thought to have lung cancer at the time they were interviewed, but who were finally proved not to have it, no significant difference in the previous incidence of any of the respiratory illnesses was detected. This last group contained a high proportion of patients with other respiratory diseases so that the results can be explained either if chronic bronchitis and pneumonia predispose to a whole group of respiratory disorders, *including bronchial carcinoma, or if patients with respiratory* disorders recall previous chronic bronchitis and pneumonia more readily than do patients with diseases in other systems Finke (1956) studied the histories of 76 patients with histologically confirmed bronchial carcinoma diagnosed at one hospital in New York State since 1940. He obtained data from the hospital records, by personal interview with the patient or with his relatives or by questionnaire to 'whoever might have had pertinent knowledge, including institutions in which the patient had been hospitalised in the past'. In 50 cases, he was able to obtain what seemed likely to be complete information and he compared these histories with those obtained directly from 50 in-patients of similar ages and from 271 out-patients with other broncho-pulmonary diseases Of the patients with lung cancer 70 per cent had been affected by a chronic chest disease for at least 10 years before the discovery of the cancer (22 had had chronic bronchitis, 8 chronic asthma, 5 proved or *suspected tuberculosis* and one silicosis); of the 'control' in-patients only 24 per cent had had a similar chronic chest disease (9 chronic bronchitis, 2 chronic asthma and 1 tuberculosis) Comparison of the two groups with regard to the past history of influenza in 1918–20, non-influenzal pneumonia or multiple attacks or severe respiratory illnesses again showed a marked difference; there was, however, relatively little difference between the incidence of these latter illnesses among the lung cancer patients and the out-patients with broncho-pulmonary disease. Wynder, Bross and Cornfield (1956) reported on the past histories of women with lung cancer They obtained data for 105 patients, *either* by personal interview or by questionnaire to the relatives, and compared the results with those obtained from 1,304 other female patients interviewed personally. The incidence of tuberculosis and pneumonia uncom*plicated by bronchitis was the same in both groups,* but a history of chronic bronchitis was obtained in half the patients with squamous carcinoma of the lung and this was appreciably more than was found among patients with other histological types of the disease (27 per cent) or among the control patients with other diseases (16 per cent). A difference in this respect between the various *histo*logical types was also reported by Lea (1952) who found that *long-standing* pulmonary symptoms were recorded for 22 per cent of men with squamous

per cent for men with oat-cell

among a group of men with

only for chronic bronchitis

Case and Lea (1955) studied men who had been invalided from the services during the first world war for chronic bronchitis and compared them with men who had been invalided for mustard gas poisoning or for loss of a limb. Over the following 30 years, men invalided for chronic bronchitis suffered a lung cancer mortality which was similar to that suffered by the men invalided for mustard gas poisoning, and which was double that experienced by other men in England and Wales of the same ages. Men invalided for loss of a limb, on the other hand, suffered a mortality which was close to normal. Since the men who had been invalided for gas poisoning suffered almost uniformly from chronic bronchitis, Case and Lea concluded that the effect in this group was probably also attributable to bronchitis rather than to any direct carcinogenic effect of the gas.

The interpretation of these observations is uncertain. That there is some association between chronic bronchitis and lung cancer is clear, but it does not necessarily follow that the association is direct. Several investigations have shown that there is a fairly close association between chronic bronchitis and cigarette smoking (Oswald, Harold and Martin 1953, Palmer 1954, Doll and Hill 1956; Ogilvie and Newall 1957) and since the association between lung cancer and smoking is much stronger than the association between cancer and bronchitis, it may be thought that the association between the two diseases is indirect and results wholly from the fact that both are associated with smoking. That this may not be the complete explanation is, however, suggested by the observation that bronchitis is more closely related to squamous cancer than to the other histological types, whereas smoking appears to be related equally to all types other than adenocarcinoma. A further difficulty in assessing the results is that both chronic bronchitis and lung cancer appear also to be related to atmospheric pollution. How far this could account for the observations which have been made is, however, impossible to assess because the available data are insufficiently precise.

The evidence linking the origin of the disease with scarring and with bronchial and pulmonary infections other than chronic bronchitis is so far almost entirely topographical. Examination of patients' past histories has failed to provide any support for the view that healed tuberculosis plays any part in the production of the disease. Unfortunately, there has not yet been a sufficiently prolonged and extensive follow-up study of the mortality among patients who have recovered from pulmonary tuberculosis for any direct evidence to have been obtained. At the present moment it must be concluded that the role of respiratory infections in predisposing to lung cancer is uncertain.

HEREDITY

Very few studies of lung cancer in relation to heredity have been made. It has been shown that lung cancer is unrelated to the ABO blood group system (Roberts 1957), but there are no data which would allow an estimate to be made of the importance of hereditary factors in general. This lack of interest is presumably due to the fact that the incidence of the disease is belie

to have increased so greatly within two generations. But even though it is clear that hereditary factors cannot be predominant, it is possible that they may play an important part in determining the susceptibility of the individual to other and changing factors in the environment.

That cancer proneness varies has been demonstrated unequivocally in animals. It is probable that it depends on the effects of large numbers of genes and it may be assumed that with each type of cancer proneness will show a wide variation and be distributed in a frequency curve of more or less normal type (Huxley 1956). Such an assumption would account for the lack of obvious heredity in human cancer in general, for in such circumstances inbreeding over many generations would be necessary to reveal the specific genetic basis of the various types of tumour. It also allows for the observation that incidences of up to 100 per cent may be produced by extremely intense exposure to some occupational hazards, while exposure to lower intensities or for shorter periods may result in only a low incidence.

It is, therefore, reasonable to assume, as a working hypothesis, that individual susceptibility to lung cancer varies; but whether the extent of the variation is sufficient, under present conditions, to make an important difference to the risk of developing the disease is entirely unknown. An answer should eventually be provided by studies such as those now being carried out by the Danish Cancer Registry (Nielsen and Clemmesen 1957). In this study, the doctor is required to state, at the time of notifying the disease, whether or not the cancer patient is a twin; if the patient is a twin, further information is then requested about the sib. In 14 years, 336 cancer patients have been notified whose twin sibs were alive in Denmark and not already notified as having had cancer. Since then, 14 of the twins have developed cancer, whereas at national rates 12·5 cases would have been expected. Three of the cancers were in concordant sites (large intestine, heart and cervix uteri) and 0 9 concordant cases were expected. The data support what was already clear from other studies on individual types of cancer, that there is no significant inheritance of cancer proneness in general; but they are as yet too few for any useful conclusions to be drawn about the extent of the hereditary variation in susceptibility to specific types

CHAPTER IX

THE AETIOLOGY OF CARCINOMA OF THE LUNG: CONCLUSION

RICHARD DOLL

FROM the work which has been reviewed in the preceding chapters a fairly distinct picture of the aetiology of the disease is beginning to appear. Several 'causes' have been recognised in the sense that the conditions under which the disease is produced have been described, but the substances directly responsible have not been identified in every case. In Britain, the most important factor is the smoking of tobacco—and perhaps almost exclusively the smoking of cigarettes. Its importance may be gauged by calculating the mortality which would occur if the whole population were subject to the death rates which have been estimated for non-smokers. Various estimates have been made, but it seems unlikely that, in the absence of smoking, the total male mortality would be more than 10–20 per cent of its present figure, while the female mortality might be approximately half.

Of the remaining cases some are due to specific hazards associated with particular industries. With the exception of the gas-producing industry, however, the numbers of men employed in the industries with an established risk are small and the proportion of the total cases attributable to occupational causes is unlikely to be large.

The evidence with regard to atmospheric pollution is less clear. Part of the difference in mortality between town and country may be attributed to differences in the extent of cigarette smoking but part—and perhaps a substantial part—may be attributed to the pollution of the atmosphere which is characteristic of towns. According to one estimate, derived from data collected in and around Liverpool, this factor may be responsible for nearly two-fifths of the male mortality in Liverpool; according to estimates derived from other data, however, the mortality specifically attributable to an 'urban factor' may be very small. In so far as atmospheric pollution is a cause of lung cancer it would seem that, in Britain, the carcinogen was more likely to be derived from chimney smoke than from the fumes of motors.

Other causes must undoubtedly also exist. It is conceivable that a few cases could be due to the radioactivity normally present in the external environment, but there is no direct evidence that this is so. If (as is possible) there is a threshold dose below which no cases are produced, the small amounts of radioactivity normally present would be expected to be innocuous. The part played by infection, and the resultant reaction and scarring in the lung tissue, also remains to be elucidated. Anatomical studies suggest that peripheral cancers may, not infrequently, arise in direct association with pulmonary scars,

but, with the exception of a doubled incidence with chronic bronchitis, it has not yet been possible to demonstrate an increased incidence following any specific type of pulmonary infection Genetic differences may also be presumed to play some part in determining the susceptibility of individuals to any or all of the environmental causes.

Not all the histological types of the disease are equally related to all the factors which have been described. Cigarette smoking, for example, appears to be unrelated to the production of adenocarcinoma of the lung, although it is closely related to the production of both squamous and oat-cell carcinomas Data with regard to the industrial cancers are conflicting. Some appear to include a substantial proportion of adenocarcinomas, but others (*e.g.*, those due to radioactivity) have been almost invariably squamous or oat-celled.

Differences in the incidence of the disease among men and women and between different countries, and the very great increase in incidence which has been observed over the last 3 to 4 decades, may be largely accounted for by differences in the consumption of cigarettes and in the degree of exposure to the hazards associated with specific industries. A more exact assessment would require knowledge of facts which is not now available; that is, of the true extent of the change in incidence of the disease, of the distribution of cigarette smoking at different periods of time and of the fundamental mechanism of carcinogenesis.

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SECTION THREE

THE PATHOLOGY OF CARCINOMA OF THE LUNG

CHAPTER X

ORIGIN AND APPEARANCES OF CARCINOMA OF THE LUNG

K. F. W. HINSON

THIS discussion on the morbid anatomical aspects of carcinoma of the bronchus will be based mainly on material from surgical excisions In such specimens the disease is necessarily in its earlier stages, and the route of extension and sequence of metastasis in the regional lymph nodes may be studied Contralateral and distant spread can only be determined from post-mortem examinations It is generally considered that the squamous cell type is the least malignant form of the disease and the proportion of such growths in surgical series will be high (Table XXIII) On the other hand, if it has been

TABLE XXIII

The Histological Type of 211 Resected Specimens (London Chest Hospital)

	Totals	*Male*	*Female*	*Sex ratio*
Squamous-celled	119 (56%)	112	7	16 1
Adenocarcinoma	24 (11%)	17	7	2 4 1
Undifferentiated	58 (28%)	53	5	10 6 1
Oat-celled	10 (5%)	7	3	2 3 1
	211 (100%)	189	22	8 6 1

possible to excise a highly malignant tumour, the pattern of metastasis may have already developed. The frequency of cell types in necropsy and operation series should only be compared if they are derived from comparable populations during the same period of time The discrepancies which exist between two such series are illustrated in Table XXIV, modified from Walter and Pryce (1955*b*) Here the histological classification was made by the same observers on unselected and consecutive specimens obtained during the same period.

ORIGIN OF THE TUMOURS

All ... from the epithelium of the ... and Day (1937) have shown ... birth Flattened cells have been demonstrated within the alveoli by metallic impregnation techniques, but they bear no resemblance to the cell types of human tumours The bronchial epithelium has a tendency to undergo metaplasia to the squamous type in response to chronic irritation or infection The intact epithelium covering a benign adenoma is usually squamous Tuberculosis of the bronchus, either a

TABLE XXIV

Incidence of the Main Histological Types in a Necropsy Series of 159 cases and a Surgical Series of 207 Cases (Modified from Walter and Pryce 1955b)

Histological type	*Necropsy series (per cent)*	*Surgical series (per cent)*
Squamous-cell carcinoma	20 1	60 4
Adenocarcinoma	28 3	15 5
Oat-cell carcinoma	37 1	15 9
Polygonal-cell carcinoma	10 7	7 7

superficial ulceration, or associated with an underlying adenitis, frequently heals with such a change Figure 20 shows squamous metaplasia in the bronchus of a child aged 18 months suffering from tuberculous hilar nodes Persistent cavities, both of tuberculous and pyogenic origin, if they become epithelialised are lined by cells which are squamous in type, and which have spread from the broncho-cavitary junctions.

In an investigation designed to discover any changes in the epithelium of the larger bronchi which might be related to smoking habits Auerbach *et al*

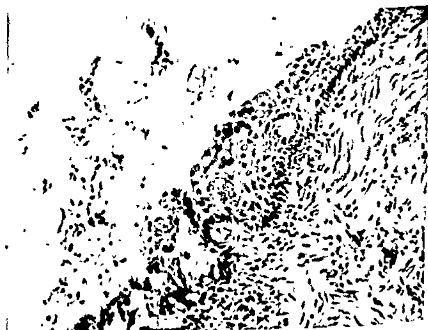


FIG 20

Squamous metaplasia of bronchial epithelium From a child aged 18 months suffering from tuberculous hilar adenitis

(1957) examined very large numbers of sections from the bronchial trees of a series of post-mortem cases, not all the patients had suffered from bronchial carcinoma They distinguished four types of change (1) Basal cell hyperplasia, in which ciliated cells persisted, but there were three or more layers of the basal cells (2) Stratification, that is when the ciliated columnar cells had disappeared and there was flattening of the surface layers (3) Squamous metaplasia, when the whole thickness of the epithelium was involved (4) Carcinoma *in situ*, when there was disorganization of the usual layers and the cells themselves varied in shape and size and in the staining properties of the nucleus, although the basal layer remained intact (Fig 21) Each of these changes, though present in a small proportion of non-smokers, was more frequently observed in smokers, and most frequently in those who had a bronchial carcinoma

Metaplasia may also be noted in those bronchioles which persist in areas of diffuse fibrosis resulting from tuberculosis or asbestosis There are many reported instances of small peripheral carcinomata arising in fibrous scars (Stewart and Allison 1943; Peterson, Hunter and Sneedon 1949, Prior and Jones 1952; Raeburn and Spencer 1953) A high incidence of bronchial

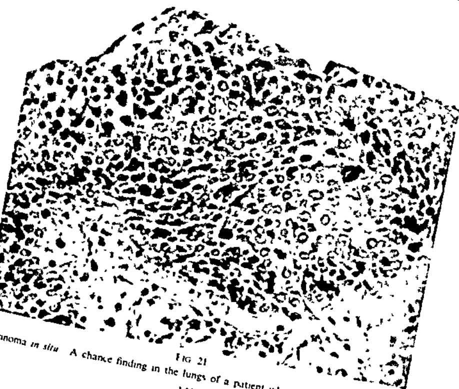


FIG 21

…noma *in situ* A chance finding in the lungs of a patient who died of pneumoconio…

carcinoma in asbestosis has been recorded by Gloyne (1951). It is probable that the ease with which the bronchial and bronchiolar epithelium undergoes metaplasia of differing degrees of differentiation explains both the frequency and the pleomorphism of squamous-celled tumours.

Squamous metaplasia also occurs in adenocarcinomas of bronchial origin Walter and Pryce (1955*a*) found this change in some degree in 19 per cent of their excised specimens, and in 12 per cent of those obtained at autopsy. In two cases the metaplasia was so extensive that the primaries were considered to be of the squamous type, but lymph node metastases were adenocarcinomatous. They quote Phillips, Basinger and Adams (1950), who found squamous metaplasia in the 9 adenocarcinomas they examined. The change may also be detected in 'oat-cell' growths and those formed of mainly polygonal cells (Walter and Pryce 1955*a*).

Histological Types

The pleomorphism of bronchial carcinomas is notorious. In a necropsy series of 84 cases, Willis (1948) examined an average of 6 blocks from each



Fig 22
Squamous-celled carcinoma.

tumour or its metastases, and found a variable histological pattern in 28 per cent. However, such difficulties in classification should not deter an attempt, as, together with a study of the extent of spread and vascular involvement, it may help in giving a reliable prognosis in surgical cases The difficulty lies in the large number of terms which have been applied to those tumours which are not clearly either of the squamous-celled or adenocarcinomatous types Both are usually easily recognizable although the metaplastic changes in the

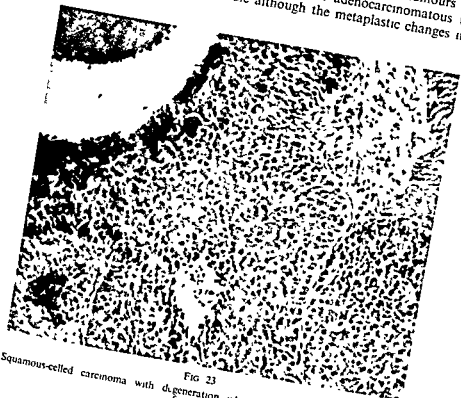


FIG 23
Squamous-celled carcinoma with degeneration which suggests adenocarcinomatous formation

tumour itself may cause doubt unless an adequate microscopic survey of the tumour and its metastases is made It is suggested that the following classification of histological types be employed. (1) squamous celled, (2) adenocarcinoma, (3) undifferentiated which will include a small number of highly malignant 'oat-cell' growths

Squamous Carcinomas

Microscopic sections of squamous-celled carcinomas show rounded or oval processes of recognizable squamous cells Keratinization is frequent and epithelial pearls may be formed The fibrous stroma is characteristically abundant (Fig. 22) Areas of degenerative softening and necrosis of both

carcinoma in asbestosis has been recorded by Gloyne (1951). It is probable that the ease with which the bronchial and bronchiolar epithelium undergoes metaplasia of differing degrees of differentiation explains both the frequency and the pleomorphism of squamous-celled tumours.

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Squamous-celled carcinoma with degeneration which suggests adenocarcinomatous formation

tumour itself may cause doubt unless an adequate microscopic survey of the tumour and its metastases is made It is suggested that the following classification of histological types be employed (1) squamous celled, (2) adenocarcinoma, (3) undifferentiated which will include a small number of highly malignant 'oat-cell' growths

Squamous Carcinomas

Microscopic sections of squamous-celled carcinomas show rounded or oval processes of recognizable squamous cells Keratinization is frequent and epithelial pearls may be formed The fibrous stroma is characteristically abundant (Fig 22) Areas of degenerative softening and necrosis of both

elements of the growth are common in larger tumours. Occasionally an island of squamous cells may undergo central softening and replacement by polymorphonuclear leucocytes and produce a false appearance of an adenocarcinoma or of squamous metaplasia in such a growth (Fig 23). Further examination of the section will, however, show the true squamous nature of this tumour.



FIG 24
Adenocarcinoma

Adenocarcinomas

Adenocarcinomas usually have the characteristic microscopic picture of tubule formation or glandular spaces (Fig 24). Mucus formation is almost universally demonstrable by appropriate staining techniques. The individual cells have an opaque cytoplasm which may vacuolate, and the vesicular nucleus is often applied to one side. Reported instances of columnar-celled carcinomas are probably examples of this type, which may not always show acinar formation

Such differing degrees of structural rather than cytological differentiation seem to be habitual in this type of growth There has been debate over the origin of the 'alveolar-celled' carcinoma. In this condition the lung is consolidated by neoplastic infiltration, and to the naked eye presents as a white pneumonia. In sections the alveolar walls are seen to be lined by columnar mucus-secreting cells, usually in a single layer (Fig 25). Confirmation of the



FIG 25

'Alveolar cell' carcinoma Neoplastic cells lining the walls of the alveoli which are outlined by deposits of carbon From the lung of a coal-miner who died of pneumoconiosis

persistence of alveolar walls may be given by carbon dust deposits within them Desquamation may result in the alveoli being filled with tumour cells, but more frequently they are distorted by large quantities of secreted mucus The usurpation of the alveolar wall as a stroma is a common mode of intrapulmonary extension by adenocarcinomas with an obvious bronchial origin The 'alveolar cell' tumour involves the lymphatics widely at an early stage The condition is, therefore, a malignant one and the term 'adenomatosis' should not be used As the affected areas may be multilobar, or even bilateral, a multicentric origin has been postulated However, the extensive lymphatic invasion makes this explanation unnecessary and it is only the difficulty in demonstrating an undoubted bronchial or bronchiolar primary which justifies the separation of the condition from the common bronchial adenocarcinomas (see also p. 178)

Undifferentiated Carcinomas

When the squamous and adenocarcinomatous growths have been identified, in all series there will remain some which cannot be classified in spite of adequate material, and staining technique In this group there will be many untypable examples of the previous ones, and it is better to classify them as undifferentiated carcinomas rather than apply a description of the cell shape or size Both these features will vary with the pleomorphism of all bronchial carcinomas and the degenerative tendencies inherent in all malignant tumours

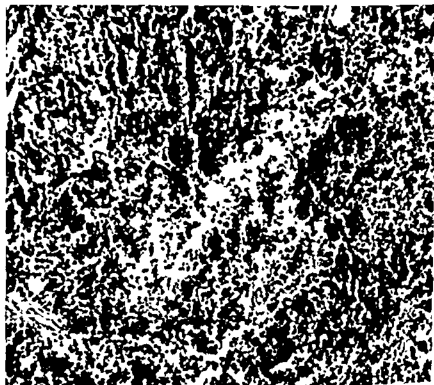


Fig 26
'Oat-cell' carcinoma

[illegible] it avoids the use of such [illegible] the 'oat-cell' growth is a separate entity, as the most malignant form of the disease, and separate it in their discussion. This form of growth is composed of uniformly small cells with a very scanty stroma formation (Fig 26) The nuclei are deeply stained, rounded or oval in shape and appear almost to fill the cell so that the cytoplasm is either indistinguishable or seen as a very thin

circumferential ring. From its microscopic appearance the confusion with a lymphosarcoma prior to Barnard (1926) was understandable. As it is usually of central origin, with early massive lymph node involvement, the post-mortem appearance would suggest a lymphatic origin. The origin of the 'oat-celled' type from the deeper layers of the bronchial epithelium is well illustrated by Walter and Pryce (1955*a*). This paper also draws attention to the frequent occurence—almost half in their 33 examples—of adenocarcinomatous or rosette formation in this type. Although the cells were all characteristically small and 'oat-like' without demonstrable mucus, they were separated by Walters and Pryce into 'differentiated' and 'undifferentiated oat-cell' growths. Differences in behaviour between these two sub-types are not suggested. There was nothing to suggest a neuroblastomatous origin in those showing rosette formation.

SITE OF ORIGIN OF THE TUMOURS

The anatomical site of origin of a carcinoma may influence the development and course of the disease, so that it is important to locate it as accurately as possible. Unfortunately, there is no universally accepted definition of central and peripheral tumours, and except for the very smallest ones it may be impossible to determine their exact point of origin. There are also divergent views on prognostic differences in the two groups. Thus, Tuttle and Womack (1934) maintain that peripheral tumours arising in relation to the easily accessible pleural lymphatics drain directly to the hilum giving rise to early lymph node metastases. Wiklund (1951) holds the opposing view, quoting the operability rate as well as the incidence of metastases. In his surgical series 51 per cent of the peripheral growths were operable and a third of the specimens showed lymph node involvement, only 37 per cent of the central tumours were resected, and of these 58 per cent involved the regional lymph nodes.

Rosenblatt and Lisa (1956) defined three groups. (1) Hilar, in which the origin is in the main or lobar bronchus and also in the segmental ones at, or near, their origin, (2) Mid-zonal, in which the growth arises more distally and yet 'some distance' from the pleura; (3) Peripheral, arising from the bronchi and bronchioles immediately beneath the pleura. It is pointed out by Walter and Pryce (1955*b*) that a tumour arising in a bronchiole adjacent to a main bronchus may present radiographically as a hilar shadow. Unless the extra-bronchial extension of such a growth is minimal it will be impossible to determine its essentially peripheral origin. Walter and Pryce also define three sites of origin. (1) Central, those growths starting in a large nominate branch from the point of origin of the main bronchus to the point of division of the segmental bronchus; (2) Intermediate, beginning in a branch of a nominate bronchus which is visible to the naked eye, and (3) Peripheral, arising in the minute distal bronchi and bronchioles. They were certain of the exact site of origin in 59 per cent of their 207 resected cases. In a further 18 per cent the site was probably located, leaving 22 per cent of undetermined origin. Wiklund

(1951), who mentions the difficulties in localizing intermediate growths, describes two types: central, tumours arising in the large bronchi; and peripheral, those which do not arise from a macroscopically visible bronchus. He notes the tendency of the central tumours to be infiltrative and occlude the major bronchus of origin, whereas the peripheral carcinomas are expansive in their mode of growth. Wiklund considers therefore that the 'non-circumscribed' and the 'circumscribed' tumours of Rabin and Neuhoff (1943) correspond respectively with his two types.

Nohl (1956) in his description of surgical specimens makes a practical clinical distinction by classing as central those growths which were visible at bronchoscopy, and, following dissection of the specimen, those cases in which it was considered that the growth should have been seen. Table XXV shows

TABLE XXV

The Site and Histological Type of the Tumour in 211 Resected Specimens (London Chest Hospital)

	Total	*Site of tumour*		
		'Peripheral'	*Central*	
			Total	*Biopsy positive*
Squamous	119	44	75	66
Adenocarcinoma	24	18	6	6
Undifferentiated	58	30	28	27
'Oat-cell'	10	2	8	8
Total	211	94	117	107

the proportions of each histological type which were found to be central It is probable that the number classed as 'peripheral' is too low, as intrabronchial extension towards the hilum will result in a tumour that has arisen more distally being classed as central Nevertheless, it tends to confirm the view that squamous cell tumours are more often central, and that adenocarcinomas are much more frequently 'peripheral' *The majority of 'oat-cell' growths are within the* range of the bronchoscope.

Table XXX indicates that if all histological types are considered together, the central growths have a higher rate of lymph node metastasis and venous involvement.

MACROSCOPIC APPEARANCES

In its earliest stage a central growth presents as a sessile intrabronchial excrescence, but even before the bronchus is occluded distal bronchiectasis and infection may occur (Figs. 27, 28). As the disease progresses the intra-bronchial portion may form an elongated polyp several centimetres in length



FIG 27

Thin section of a pneumonectomy specimen Bronchiectasis in basal branches distal to the growth

without corresponding involvement of the bronchial wall, or the whole circumference of the mucosa may be infiltrated and become raised and irregular so that again the lumen is obliterated. Combinations of varying degrees of polyp formation and mucosal involvement are, of course, common Even in the later stages when the major part of the lobe is affected by infiltration, collapse and sepsis the branch which was primarily involved by the tumour



FIG 28

Thin section of a pneumonectomy specimen Central tumour causing gross bronchiectasis in middle and lower lobes

may be indicated by the distension bronchiectasis which it caused De Nevasquez and Haslewood (1954) have described lipoid pneumonia in the lung distal to carcinomas of the bronchus which they ascribe to 'alveolar injury'; but the infection may be so severe that destruction of the lung tissues may follow and an actual lung abscess be formed (Fig. 29) Such a pyogenic abscess due to bronchial obstruction differs from a neoplastic abscess in which necrosis, infection and excavation of the extrabronchial portion of the tumour has developed (Fig. 30). In the latter, the wall is a wide zone of white, obviously

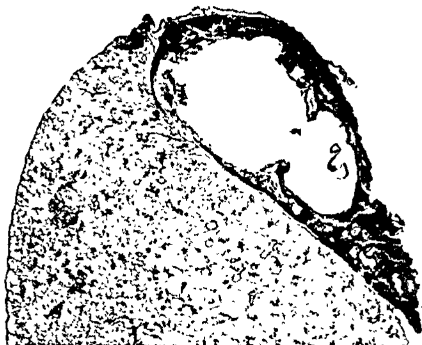


Fig 29
Thin section of a pneumonectomy specimen Pyogenic abscess replacing upper lobe, resulting from central tumour



Fig 30
Thin section of a pneumonectomy specimen. Cavitating peripheral tumour

neoplastic, infiltration; the inner surface is grossly irregular and the outer edge shows the scalloped outline of the advancing carcinoma. Such neoplastic abscesses formed by central growths usually communicate with a major bronchus.

Peripheral tumours usually remain roughly spherical until their diameter is some 4–5 centimetres, but the cut surface shows a characteristic circumferential scalloped edge without encapsulation (Fig. 31). (This may also be seen

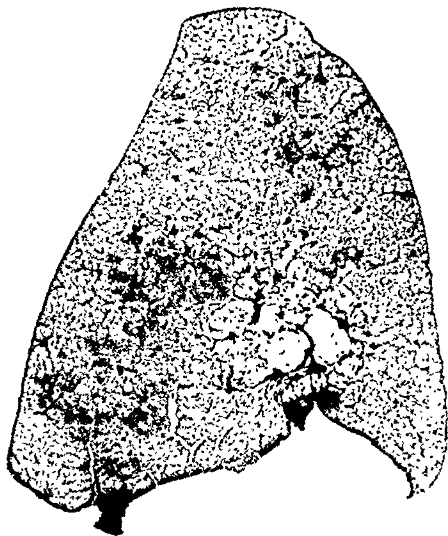


FIG 31
Thin section of a lobectomy specimen. Peripheral carcinoma with puckered diaphragmatic surface

radiographically (Simon 1956; Rigler 1955, 1957)) The absence of peripheral fibrosis and small satellite areas of caseation assists in immediate distinction of such early carcinomas from caseous tuberculous foci Peripheral tumours are usually free from obstructive or infective changes but when, as they often do, they attain a tremendous size replacing almost a whole lobe, central softening and excavation may follow. Such neoplastic abscesses in peripheral growths will, however, also present the same irregular wall as the central type except that the outer boundary may consist of pleura alone. The occurrence of macroscopic mucus will often allow an immediate diagnosis of an adenocarcinoma to be made.

Spread within the Lung

All peripheral carcinomas and the majority of central ones show extrabronchial extension when the specimen is resected. There is circumferential infiltration which proceeds too rapidly for encapsulation, and in microscopic sections from most cases, growths of neoplastic cells may be seen in advance of the apparent edge This mode of progression occurs in all the histological types but in particular the cells of an adenocarcinoma seem to find the alveolar walls a suitable supporting framework, so that in the zone of advancing growth the picture of the 'alveolar cell' carcinoma is presented The normal pleura apparently acts as a bar to further direct extension but its lymphatics are frequently permeated. There is a fibrinous exudation over the lobe or segment involved, but actual ulceration of the growth is rare. There are exceptions, tumours arising in the apex of the upper lobe may involve both visceral and parietal pleura and spread outwards to involve all the structures of the chest wall Perhaps the presence of long-standing adhesions with the development of lymphatic channels between the adjacent layers does not allow the visceral pleura to maintain its usual limiting function Most of the growths which behave in this manner are of the squamous-celled variety and their slow extension may give time for such pleural symphysis to form, but as the condition is unusual in situations other than the apex of the upper lobe this possibility must be remote. When the extrabronchial spread has involved another lobe the fissure is always closed by adhesions

CHAPTER XI

THE SPREAD OF CARCINOMA OF THE LUNG

K F. W. Hinson

Intrathoracic Spread

INVOLVEMENT of the lymphatic channels with subsequent metastasis in the hilar lymph nodes is the most important mode of intrathoracic spread. Lymphatic embolism, permeation and probably also retrograde embolism all play their part Even in bronchial biopsy specimens, involvement of the mucosal lymphatics may be recognised, and this mode of progression is one by which the intrabronchial extension proceeds in both directions. The peribronchial lymphatics are invaded at an early stage and may lead to neoplastic thickening or cuffing of the peribronchial tissues visible to the naked eye. Through these vessels the bronchopulmonary nodes are metastasised and further spread to the hilar and mediastinal groups is soon in progress. Metastasis and subsequent malignant ulceration of a lymph node into the bronchus of another segment, or even lobe, opens up further channels of infiltration This mechanism of spread to another lobe is probably responsible for the suggestion that bronchial embolism occurs (see p. 140), and suspicion that a single lung may be the seat of two primary growths. Although direct invasion of the small blood vessels can be demonstrated in the majority of cases by injection methods in the area of pulmonary infiltration, there is commonly some invasion of the perivascular lymphatics; and this is yet another pathway to the hilar and mediastinal lymph nodes The lymphatics of the visceral pleura also drain towards the hilum and their permeation in the neighbourhood of peripheral tumours has already been mentioned. Lymphangitis carcinomatosis is an extreme case of continuous lymphatic permeation (Fig 32)

Invasion of the wall of the atrium is by extension from the pulmonary vein and pericardial infiltration results either by direct spread from a contiguous metastasised lymph node, or from the involved perivascular lymphatics.

Neoplastic thickening of both the visceral and parietal pleurae associated with an effusion produces the clinical picture of a 'mesothelioma' of the pleura The neoplastic tissue enveloping the collapsed lung and replacing the parieta pleura may be a centimetre thick with nodules projecting into the effusio The nodular infiltration covering the chest wall and diaphragm may be ev thicker Although the possibility of a primary tumour of the pleura cannot denied, it is probable that the condition is caused by a particular form spread or implantation of a carcinoma elsewhere (Smart and Hinson 195 In this series the tumour was most frequently an adenocarcinoma which permeating the lymphatics, infiltrating the resulting fibrous reaction, capable of proliferation on the surface of the pleural membrane This of pleural involvement was found in association with bronchial carcinomas also with primary growths in the stomach, colon, rectum, prostate and fe

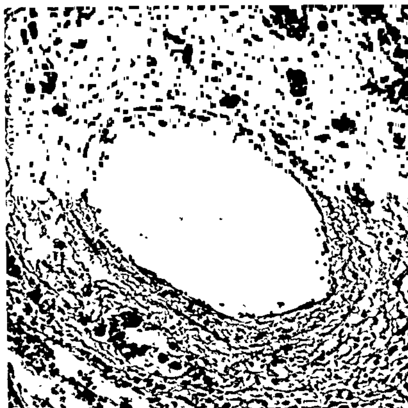


FIG 32
Malignant permeation of perivascular lymphatics

breast There was an unexplained preponderance (19 out of 24 cases) of right-sided pleural lesions, the condition occurred on that side after previous left mastectomy.

Vascular Involvement

The arterial supply of bronchial carcinomas is from the bronchial arteries (Wood and Miller 1938; Wright 1938, Cudkowicz and Armstrong 1953) By injections of coloured or radio-opaque suspensions and subsequent radiographs and microscopic sections, a diffuse supply from the bronchial arteries is demonstrable No such bronchial supply is apparent in metastatic deposits in the lung This exclusive supply is confirmed by Delarue, Mignol, Paillais and Sars (1954) who maintained that the pulmonary arteries play no part, and indeed at an early stage are narrowed or obliterated Thrombosis and re-canalisation of the pulmonary artery was noted in two instances by Cudkowicz and Armstrong. Peripheral infarction was found in 10 out of 100 pneumo-nectomy specimens by Hanberry, Cureton and Simon (1954) In two of their cases major branches of the pulmonary arteries were both infiltrated and

thrombosed. Ballantyne, Clagett and McDonald (1957) in an investigation of vascular involvement by bronchial carcinomas found microscopic invasion of the pulmonary artery in 10 out of 59 excised lobes or lungs.

Involvement of the pulmonary vein is far more frequent, and is responsible for blood-borne metastases. Aylwin (1951) found that in 40 per cent of his resected cases there was malignant infiltration of the vein wall at least as far as the intima. Ballantyne, Clagett and McDonald (1957) considered dissemination of malignant cells into the blood stream to be possible if there

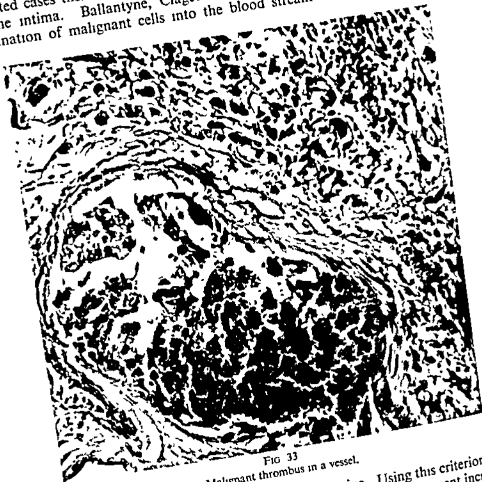


FIG 33
Malignant thrombus in a vessel.

was proliferation of tumour within the elastic lamina. Using this criterion they reported vascular invasion in 88 per cent of their cases The apparent incidence of this complication will, of course, be greater the more careful the dissection and the more serial sections that are examined. Even in large branches of the pulmonary vein close to the hilum, a polypoid formation of organised thrombus infiltrated by growth may be found in relation to intimal invasion (Fig. 33) Such malignant thrombi may occur some distance proximal to the tumour mass, as a result of vascular involvement from an adjacent metastasized lymph node. Examination of sections from situations where the anatomical relationship

TABLE XXVI

The Extent of the Primary Tumour Related to Lymph Node Metastases and Venous Involvement in 211 Resected Specimens (London Chest Hospital)

Extent of primary	Total	No node metastases	Node metastases*				Venous involvement
			Total	Med. Hilar Br pul	Hilar Br pul	Br pul only	
SQUAMOUS							
Group A†	50	19	31	12	14	5	12
Group B	44	14	30	19	8	3	9
Group C	25	8	17	8	8	1	13
Total	119	41	78	39	30	9	34
ADENOCARCINOMA							
Group A	6	1	5	3	2	0	0
Group B	11	5	6	4	1	1	5
Group C	7	0	7	6	1	0	4
Total	24	6	18	13	4	1	9
UNDIFFERENTIATED							
Group A	16	5	11	8	3	0	2
Group B	27	8	19	12	7	0	11
Group C	15	1	14	13	1	0	11
Total	58	14	44	33	11	0	24
'OAT-CELL'							
Group A	5	1	4	2	2	0	1
Group B	1	0	1	1	0	0	1
Group C	4	0	4	4	0	0	4
Total	10	1	9	7	2	0	6

* Med = mediastinal Br pul = broncho-pulmonary
† Group A = tumour limited to the lung
Group B = tumour invading pleura
Group C = tumour invading mediastinum or chest wall

suggests this possibility should never be omitted Table XXVI (which is shown in condensed form in Tables XXVII, XXVIII) shows the proportion of specimens in which intimal involvement was demonstrated in this laboratory (Fig. 34)

Lymph Node Involvement

Attempts have been made to indicate the route and sequence of intrathoracic lymph node involvement. In post-mortem series the incidence of such metastases is as high as 97 per cent (Olson 1935). In surgical series it will vary with the extent of the growth, and the completeness of the histological examination of the nodes. Serial sections are essential

In such a series from this laboratory, lymph node metastases were demonstrated in 75 per cent by Nohl (1956), who indicated important differences in the route of dissemination between the two sides (Figs 35, 36). This type of investigation is difficult, if the growth has crossed a fissure further pathways

TABLE XXVII

Venous Involvement Related to the Extent of the Primary and the Histological Type in 211 Resected Specimens (London Chest Hospital)

	Total	Venous involvement	
		Number	Per cent
EXTENT			
Group A	77	15	(19)
Group B	83	26	(31)
Group C	51	32	(63)
HISTOLOGICAL TYPE			
Squamous	119	34	29
Adenocarcinoma	24	9	(38)
Undifferentiated	58	24	(41)
'Oat-cell'	10	6	—
Total	211	73	35

Percentages in brackets are based on less than 100 cases
Group A = tumour limited to lung
Group B = tumour invading pleura
Group C = tumour invading mediastinum or chest wall

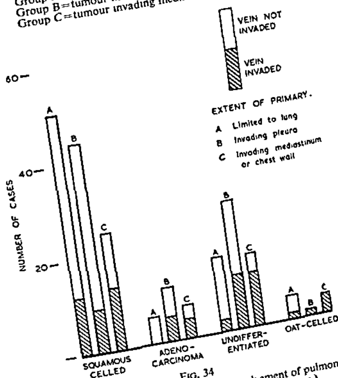


FIG. 34

Proportions of excised carcinomas with involvement of pulmonary veins (211 cases London Chest Hospital series)

are opened, and the possibility of retrograde embolism cannot be excluded. Tumours in the right lower lobe metastasise in those lymph nodes around the lower part of the main bronchus and occasionally upwards to nodes related to the segmental branches of the upper lobe branches The sub-carinal and para-oesophageal nodes are often involved Nohl stresses the importance of the group around the lower part of the main bronchus. These are the nodes lying between the upper lobe bronchus and the branches to the middle lobe and apical lower segment; they have been called the 'lymphatic sump of the right lung' by Borrie (1952). This term is significant, because the group is also involved by carcinoma arising in the right upper lobe Upper lobe growths also invade the para- and pre-tracheal nodes in an upward direction, but metastasis to the sub-carinal and para-oesophageal nodes is infrequent.

Nohl suggests that invasion across the fissure of the upper lobe by carcinomas arising in the lower lobe is more common on the left side than the right, but in the growths confined to the left lower lobe the pathway of metastasis is upwards The node above the apical branch is commonly implicated, as are the para-oesophageal and pulmonary ligament group Those nodes around the bronchus and the sub-carinal group also show deposits Left upper lobe tumours also give rise to metastases in the nodes above the apical lower bronchus and the main bronchus, but, unlike right upper lobe growths, do invade the sub-carinal group Involvement of this group by left upper lobe carcinomas leads to upward spread in the right superior mediastinum.

A simple but informative classification has been proposed by Salzer, Wenzl, Jenny and Stangl (1951), which takes into account the extent of the growth within the lung and also the degree of lymph node involvement.

Group A The growth is confined to the lung

Group B The growth has extended to the pleura at the site of adhesions, but the pleura itself is not infiltrated

Group C There is direct involvement by continuity of the chest wall or mediastinal structures

The degree of lymph node metastasis is indicated by five categories of increasing severity.

0 No metastases

1 Broncho-pulmonary nodes involved

2 Hilar nodes involved.

3 Mediastinal nodes involved

4 Extrathoracic metastases present (not necessarily of lymphatic origin).

Table XXVI summarizes the findings in 211 consecutive lobectomy or pneumonectomy specimens following this classification with one modification· a tumour was placed in group B if the infiltration had reached the pleura even though overlying adhesions were not present. This may have produced an apparent anomaly in results recorded for adenocarcinomas, which will be mentioned later. The incidence of involvement of major branches

of the pulmonary vein by growth as far as the intima, with or without a
mal[illegible] [illegible]fferences in the behaviour of
the [illegible] Fig. 37)
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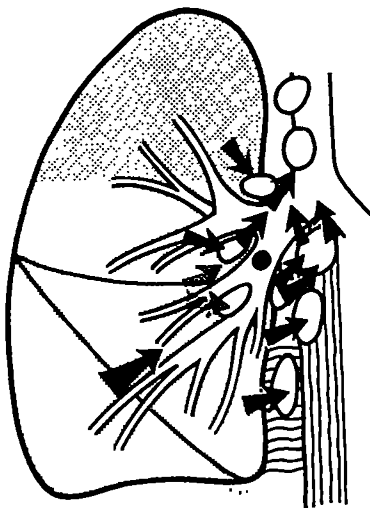


FIG 35 [illegible] nodes

Right lung

Bl

Bl

Red [illegible]

[illegible] undifferentiated type occupy intermediate positions With
[illegible] increasing extent of the
[illegible] Group C) In
[illegible] ie proportion
the other types, undifferentiated and [illegible]
with mediastinal node involvement is very high in Group C specimens Excluding

a single adenocarcinoma, the squamous cell tumours were the only ones to show invasion of the broncho-pulmonary nodes alone. This, together with the fairly constant lymph node metastasis rate in tumours of increasing primary extent, may suggest that lymphatic dissemination in squamous-celled carcinomas is relatively slower than in the other types However, it may be necessary to

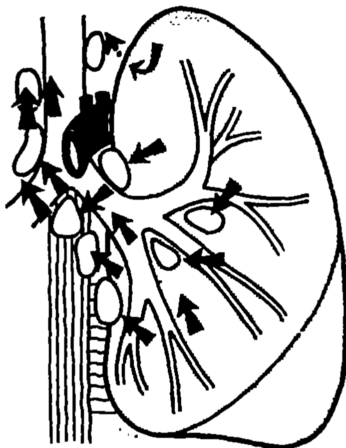


FIG 36

Left lung Diagrammatic routes of metastasis to lymph nodes (Modified from Nohl 1956)

Black arrows Routes from the lower lobe
Red arrows Routes from the upper lobe

take other factors, such as their more usual central origin, earlier production of symptoms and easier definite diagnosis, into account before this assumption of a less malignant course is made.

The Table shows a discrepancy in the behaviour of the adenocarcinomas which is perhaps more related to their site of origin than their speed of

lymphatic spread. The incidence of node metastases in those adenocarcinomas which have reached the pleura but not invaded the mediastinum or chest wall (Group B) is lower than the incidence among other histological types in this

TABLE XXVIII

The Extent of the Primary Tumour Related to Lymph Node Metastases in 211 Resected Specimens (London Chest Hospital)

Extent of primary	*Total*	*No node metastases*		*Node metastases**				
				Total		*Med Hilar Br pul*	*Hilar Br. pul*	*Br pul only*
		Number	*Per cent*	*Number*	*Per cent*			
Group A	77	26	(34)	51	(66)	25	21	5
Group B	*83*	*27*	*(33)*	*56*	*(67)*	*36*	*16*	*4*
Group C	51	9	(18)	42	(82)	31	10	1
Total	211	62	29	149	71	92	47	10

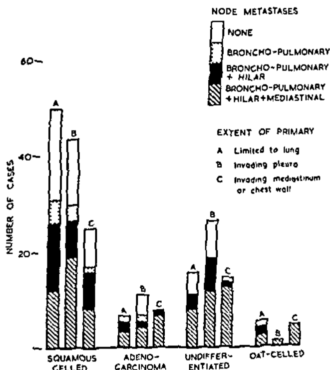


FIG 37

Extent of lymph node metastasis in 211 excised bronchial carcinomas (London Chest Hospital series)

TABLE XXIX

The Histological Type of Tumour and Lymph Node Metastases in 211 Resected Specimens (London Chest Hospital)

Histological type	Total	No node metastases		Node metastases*				
				Total		Med Hilar Br pul	Hilar Br pul	Br pul only
		Number	Per cent	Number	Per cent			
Squamous	119	41	34	78	66	39	30	9
Adenocarcinoma	24	6	(25)	18	(75)	13	4	1
Undifferentiated	58	14	(24)	44	(76)	33	11	0
'Oat-cell'	10	1	—	9	—	7	2	0
Total	211	62	29	149	71	92	47	10

Percentages in brackets are based on less than 100 cases

* Med = mediastinal Br pul = broncho-pulmonary

group Adenocarcinomas tend to arise peripherally and lymphatic spread is commonly observed microscopically More of them may, therefore, reach the pleura by lymphatic permeation before the intrapulmonary or hilar nodes are reached than in the case of central tumours.

The incidence of pulmonary vein involvement (Fig 34) rises with the extent of the primary growth This rise is least marked in the squamous cell type but striking in the undifferentiated and 'oat-cell' varieties. Whatever the explanation of the anomalies of lymph node metastases in adenocarcinomas involving the pleural lymphatics, it would seem that vascular invasion is common in these growths at this stage

Table XXX records difference in venous involvement with central and peripheral tumours The incidence of involvement is higher in the central group.

TABLE XXX

The Site of the Primary, Lymph Node Metastases and Venous Involvement in 211 Resected Specimens (London Chest Hospital)

Site of tumour	Total	No node metastases		Venous involvement	
		Number	Per cent	Number	Per cent
Central	117	26	22	46	39
'Peripheral'	94	36	(38)	23	(24)
Total	211	62	29	69	33

Percentages in brackets are based on less than 100 cases.

lymphatic spread The incidence of node metastases in those adenocarcinomas which have reached the pleura but not invaded the mediastinum or chest wall (Group B) is lower than the incidence among other histological types in this

TABLE XXVIII

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				Total		*Med Hilar Br pul*	*Hilar Br pul*	*Br pul only*
		Number	*Per cent*	*Number*	*Per cent*			
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Group B	83	27	(33)	56	(67)	36	16	4
Group C	51	9	(18)	42	(82)	31	10	1
Total	211	62	29	149	71	92	47	10

Percentages in brackets are based on less than 100 cases
* Med = mediastinal, Br pul = broncho-pulmonary.
Group A = tumour limited to lung.
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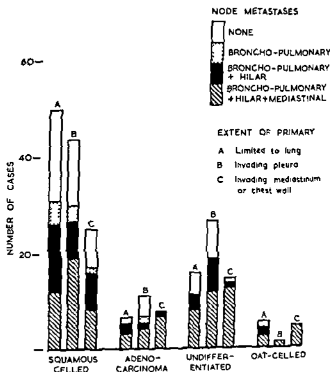


FIG 37
Extent of lymph node metastasis in 211 excised bronchial carcinomas (London Chest Hospital series)

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Total	211	62	29	149	71	92	47	10

Percentages in brackets are based on less than 100 cases

* Med = mediastinal Br pul = broncho-pulmonary

group Adenocarcinomas tend to arise peripherally and lymphatic spread is commonly observed microscopically. More of them may, therefore, reach the pleura by lymphatic permeation before the intrapulmonary or hilar nodes are reached than in the case of central tumours.

The incidence of pulmonary vein involvement (Fig 34) rises with the extent of the primary growth This rise is least marked in the squamous cell type but striking in the undifferentiated and 'oat-cell' varieties Whatever the explanation of the anomalies of lymph node metastases in adenocarcinomas involving the pleural lymphatics, it would seem that vascular invasion is common in these growths at this stage

Table XXX records difference in venous involvement with central and peripheral tumours The incidence of involvement is higher in the central group

TABLE XXX

The Site of the Primary, Lymph Node Metastases and Venous Involvement in 211 Resected Specimens (London Chest Hospital)

Site of tumour	Total	No node metastases		Venous involvement	
		Number	Per cent	Number	Per cent
Central	117	26	22	46	39
'Peripheral'	94	36	(38)	23	(24)
Total	211	62	29	69	33

Percentages in brackets are based on less than 100 cases

The Distribution of Metastases

Metastases have been found in almost every organ of the body. Ochsner and De Bakey (1942) reviewed the published reports of 2,047 necropsies. Regional node metastases were recorded in nearly three-quarters of all cases and liver metastases in about one-half (Table XXXI).

The reported incidence of metastases at each site depends, among other factors, on the source of the material and the thoroughness of the examination. For instance, in the series collected by Galluzzi and Payne (1955), the incidence of liver metastases ranged from 27 per cent to 44 per cent and of secondaries in the pancreas from 7 per cent to 27 per cent at the 8 hospitals The figures for

TABLE XXXI

The Incidence of Distant Metastases at Various Sites in Four Reports Based on Necropsy Records

Site	*Ochsner and De Bakey* (1942)	*Bryson and Spencer* (1951)	*Engleman and McNamara* (1954)	*Galluzzi and Payne* (1955)
Total cases	3,047	866	234	741
Number with metastases	—	620 (72%)	—	517 (70%)
Liver	53%	35%	38%	39%
Adrenals	20%	24%	38%	33%
Brain	16%	17%	8%	26%*
Bones	21%	13%	17%	15%
Kidney	17%	12%	28%	15%
Pancreas	7%	8%	7%	12%
Spleen	3%	4%	5%	5%
Thyroid	2%	2%	1%	4%

* Of those in whom the brain was examined.

regional node metastases in necropsy material have varied from 30 per cent (Miller and Jones 1930) to 97 per cent (Olson 1935) and in surgical material from 31 per cent (Salzer, Wenzl, Jenny and Stangl 1952) to 75 per cent (Nohl 1956) There is, however, general agreement that the regional nodes, liver, adrenal, bone, brain and kidney are the most usual sites, each being involved in more than 10 per cent of all who die of the disease; and that adrenal metastases occur in from a quarter to a third. Some recent reports do not mention metastases in the lungs themselves; but they were recorded in 23 per cent of the large series collected by Ochsner and De Bakey (1942) and in 15 per cent of the series of Engelman and McNamara (1954). Tumour tissue may reach the lung opposite to the primary through the blood stream or the lymphatics or possibly by intrabronchial spread ('embolies bronchiques'—

Letulle and Jacquelin (1924)). Stern (1954) recorded them in 17 per cent of necropsies. Pulmonary lymphangitis carcinomatosis is rare. Harold (1952) collected 154 examples from the literature and added 24 of his own. The stomach was the commonest site of the primary and the original tumour was in the lung in 23 of the 178 cases Of the 10 added by Harold, 8 were adenocarcinomas—an unusually high proportion The 'bronchiolar' cancers, which are histologically similar to the adenocarcinomas, also tend to spread widely in both lungs Secondaries in the skin are uncommon Charache (1939) found almost 3 per cent among 1,063 collected cases of bronchial carcinoma, Ariel, Avery, Kanter, Head and Langston (1950) 1 per cent among 1,109 patients, and Ochsner and De Bakey (1942) nearly 4 per cent. Rarely, metastases in the intestine have caused perforation and in the pituitary diabetes insipidus

Galluzzi and Payne (1955) studied the incidence of metastases in certain sites in relation to the weight of the organs and the blood flow through them The incidence appeared to increase with weight, though the adrenals were an outstanding exception 39 per cent of all patients having metastases had liver involvement and the mean weight of the liver is about 1,650 g ; but with the adrenals, which weigh only 12 g , the incidence was 33 per cent—almost as high *There was no simple relationship with blood flow They pointed out that the* higher incidence of adrenal metastases in young men and the fact that the few instances of ovarian metastases occurred mainly in women under 50 suggest that there may be some relationship between the metastasis rate and the biological activity of these endocrine organs However, the tumours in the adrenals may not have been carried there by the blood stream; they may have arisen by direct lymphatic spread from the primary Onuigbo (1957) studied the records of 1,000 necropsies in several Glasgow hospitals and related the side of the adrenal metastases to the side of the lung primary In 100 cases they were on the same side and in only 63 on opposite sides Moreover, when there were bilateral adrenal metastases, the larger was on the same side as the primary in 39 cases and on the opposite in 24 Adrenal metastases occur in the medulla and it is from this part that the efferent lymph vessels emerge If tumours metastasise to the adrenals by retrograde spread in lymphatics, the medulla would probably be the first portion involved It is possible that metastases in the liver and kidney also occur by lymphatic spread Onuigbo found a much higher proportion of kidney metastases on the same side as the primary Metastases are most commonly found in the intrathoracic nodes, and the upper abdominal nodes are more frequently involved than the lower (Evans 1927; Ochsner, Dixon and De Bakey 1945, Willis 1948, Onuigbo 1957) A similar decrease of involvement with increasing distance from the primary occurs with the liver, adrenals and kidneys There appears therefore, to be reasonable grounds for the hypothesis that spread to these organs occurs predominantly by the lymphatics

The incidence of brain metastases has been studied in detail by Galluzzi and Payne (1956) In 647 full necropsies there were 166 (26 per cent) with secondaries in the brain, and in 41 of these other metastases were found elsewhere in the body Moreover, in 23 patients—14 per cent of all with brain

metastases—the secondary was a single tumour mass. Meyer and Reah (1953) found cerebral metastases in 25 per cent of their necropsy cases. In 30 per cent of these there was a single tumour but in only 2 per cent was it the only metastasis in the body. In half the cases of brain involvement the secondary was in the cerebellum. Flavell (1949) found 9 per cent of single, solitary metastases (excluding regional node involvement) in 85 necropsies and in 1 case the solitary secondary occurred 2 years after pneumonectomy. There is a report of a man of 34 with a squamous lung cancer and a brain metastasis who had both tumours removed and was still alive nine years later (Flavell 1949; Thompson, personal communication).

In about a quarter of the patients dead with a lung cancer there are no distant macroscopic metastases (Bryson and Spencer 1951; Galluzzi and Payne 1955). In a few the immediate cause of death may have been direct involvement of the heart; but in most cases the mechanism of death is unknown, as indeed it is in many patients with metastases that are apparently not destroying any vital structures

CHAPTER XII

LABORATORY DIAGNOSIS

K F W Hinson

ᵀHE establishment of a definite histological diagnosis, the exclusion of conditions which may simulate a carcinoma, and the recognition of com-cations and co-existent infections are the objectives of laboratory investiga-ns

Examination of Bronchoscopic Biopsy Material

Bronchoscopic biopsy material offers the greatest opportunity for a firm ignosis to be made Table XXV shows the frequency with which positive ults may be obtained from those tumours within range of the instrument the squamous cell and 'oat-cell' cases the type of tumour is usually correctly cognised from the biopsy specimen, but some of the adenocarcinomas will placed in the undifferentiated group (The histological types in the Table : those recorded after examination of the excised specimen) It is rare for a condary deposit to present as an intrabronchial polyp but it does occur in tients suffering from a 'hypernephroma' or a carcinoma of the breast

In the laboratory all the material provided should be embedded and ial sections prepared Prolonged search may be required and even apparently rmal mucosa may show lymphatic permeation by neoplastic cells

Examination of Sputum

The examination of sputum for neoplastic cells from patients on whom onchoscopy has not been helpful is an essential step in the laboratory ignosis Philps (1954) has given the historical background to the subject om the English, American and Continental sources with a description of the chnical methods employed Each pathologist will make his own choice from ese; but for everyday use there is little doubt that wet films stained by the ethylene blue method (Schuster 1947, 1955) are the most rewarding In ses of doubt, or for record purposes, permanent films stained with haematum d eosin (Dudgeon and Wrigley 1935) or by the more complex procedures of panicolaou (1942) may be used The advantages of the wet film method are at each preparation is quickly made, the actual amount of sputum searched is rger and, most important, the suspicious cells or clumps are seen in depth This st point has been emphasised by Schuster (1955), who points out that the ll body, like the nucleus, has characteristic signs of malignancy These are·
...nce of degenerative changes
... the wet film technique.
... must be able to recognise the

cells present in sputum from patients without neoplasms, and, by making preparations from fresh unfixed specimens of tumours, be familiar with the morphology and staining properties of the malignant ones. The sputum should be placed in a Petri dish and slides made from portions with differing naked-eye appearances Bloodstained flecks and white opaque streaks should always be examined The apparently uniformly purulent sputum from a malignant abscess has white granules in it which must not be neglected. The specimen need not be completely fresh but if examination is delayed more than a day the specimen should be kept in the refrigerator.

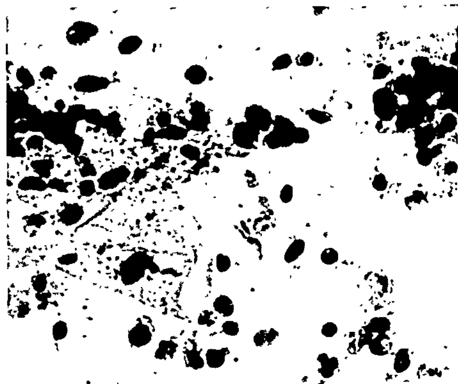


Fig 38
Streak of cells from an 'oat-cell' carcinoma in sputum

The cells from well-keratinised squamous cell growths and from 'oat-cell' tumours can be recognised with certainty; but the majority of positive specimens can be reported only as containing neoplastic cells with no opinion on their type. An 'oat-cell' growth should never be diagnosed on individual cells, for these may be quite indistinguishable from lymphocytes. The neoplastic tissue from an 'oat-cell' tumour is a clump, or more characteristically a streak of cells extending over two or more fields of the microscope (Fig. 38) In such a streak the nuclei are irregular in shape and appear to fill the cell Philps (1954) has illustrated valuable differences in the morphology of lymphocytes, which may also be present in clumps. The border of the lymphocytes can be seen, whereas

the 'oat-cells' are so closely applied that a syncytial appearance results. Minute fragments of an adenocarcinoma may also appear in the sputum (Fig 39) The preparations show a clump rather than a streak of fairly large cells with an opaque cytoplasm, often vacuolated, with a vesicular nucleus applied to one



Fig 39
Clump of cells from an adenocarcinoma in sputum.

side of the cell. In such a specimen these clumps are usually well distributed However, it is the cells from the squamous and undifferentiated types which will occur most frequently Their most striking and most constant feature is the enormous variation in both shape and size. The differences are so marked that even isolated cells may be noted when first seen with the two-thirds

objective. In methylene blue films the cytoplasm is usually greenish and the cells appear to have a firm or even doubly contoured edge. The nucleus also varies in outline, size and staining properties. It is irregular or angulated in shape and nearly always large (Fig. 40). Within any one aggregation of

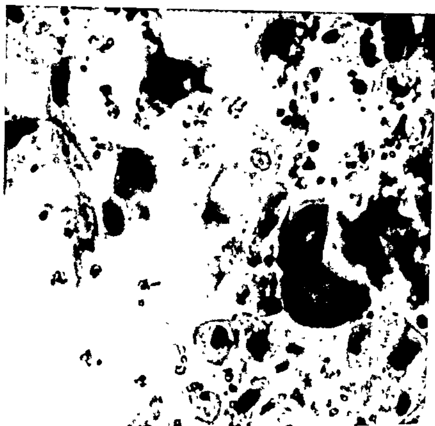


FIG 40
Malignant cells of the squamous type in sputum smear

pleomorphic cells the presence of nuclei, some of which are extremely hyperchromatic and some practically unstained, is a characteristic feature of malignancy

If the sputum of all cases of carcinoma of the lung is investigated by one of these methods, positive findings can be expected in about 80 per cent (Jennings and Shaw 1953; Philps 1954; Schuster 1955) Its practical value lies in the number of peripheral tumours—out of the range of the bronchoscope—that can be diagnosed. Malignant cells were found in 27 of the 42 peripheral tumours reported by Jennings and Shaw from this laboratory. From the 94 'peripheral' cases in the London Chest Hospital series described in this Chapter neoplastic cells were demonstrated in 44 (47 per cent) Including the 107 positive biopsies from the central group, it follows that a definite

pre-operative diagnosis was made in 151, or that only 28 per cent of the 211 patients were subjected to thoracotomy without histological or cytological evidence of a carcinoma.

Familiarity with the technique will enable a rapid diagnosis to be made of suspicious lesions received from the operating theatre. Smears should always be made while frozen sections are being prepared.

Most reports on the value of sputum examination discuss the occurrence of false positive findings. The frequency of such errors will, of course, vary with the composition of the group of cases studied and the experience of the observer. Sheets of bronchial epithelial cells are detached by the passage of the bronchoscope, and, remaining in the bronchi, undergo degenerative and inflammatory changes. They may be mistaken for a clump of 'oat-cells', so that the investigation should not be undertaken during the 7 to 10 days following bronchoscopy. The various conditions in which squamous metaplasia of the bronchial epithelium occurs offer further hazards. Long-standing tuberculosis in the elderly gives rise to particular difficulties. As the investigation is a time-consuming one, it is essential that the physician or surgeon should give full clinical details so that special care may be devoted to such cases.



Fig. 41
Punch biopsy of parietal pleura. Fibrous tissue infiltrated by an adenocarcinoma

Examination of Pleural Effusions

It is not easy to demonstrate neoplastic cells in pleural effusions occurring during the course of a carcinoma of the lung. The effusion may follow pulmonary infection or infarction and proliferation of tumour cells on the pleura is

uncommon Pleural mesothelial cells which have been shed into an effusion assume extraordinary appearances, with vacuolation, giant forms and aggregations into clumps, and extreme caution is necessary in the diagnosis of a malignant effusion on cytological grounds.

Material may be obtained by biopsy at thoracoscopy or thoracotomy. Punch biopsy of the parietal pleura may be done with a special needle (Abrams 1958). The specimen is often useful, both for the diagnosis of tuberculous effusions and for malignant infiltration of the pleura (Fig 41) (Mestitz, *Pollard and Purves 1957*).

Simple biochemical methods have not proved useful in separating infective effusions from those caused by malignant infiltration. Hitze (1955) suggested that the electrophoretic pattern of the proteins in effusions might assist in the differentiation Shaw and Brews (1956) showed in two patients with a bronchial carcinoma and a pleural effusion that the α_2 globulin level in the effusion was strikingly low in contrast to the high α_2 globulin fraction in the serum In a larger series, Watkins (1948) found this difference to be present in the majority of cases.

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SECTION FOUR

THE COURSE OF CARCINOMA OF THE LUNG

. . . I became quite tired of the difficulty of attempting to explain the phenomena observed . . . and . . . gave up all further attempts at diagnosis

Graves, R. J. (1848): Clinical Lectures on the Practice of Medicine, Vol. 2, p. 75. Dublin Reprinted by the New Sydenham Society, London, 1884

CHAPTER XIII

THE METHOD OF INVESTIGATION

J. R BIGNALL

LUNG cancer appears in varying guises to different people The physician sees it differently from the demographer and the radiotherapist from the surgeon One may think of it as a series of problems in diagnosis, another is concerned with its impact of killing on changing populations; to some it is just one cancer among the many; and to others it appears in terms of operability and survival rates. Even though it is by no means a representative sample, an unselected series of patients attending special hospitals does give a clinical picture of the disease relatively unbiased by the special interests of the various observers Such a series is the foundation of this study of the course of lung cancer, in which I have tried, in particular, to relate the clinical picture to some of the factors that are beyond the control of the patients or their doctors—age, sex, malignancy and site

SOME DIFFICULTIES OF INVESTIGATION

Inaccuracy of Hospital Records

Hospital records contain many different types of statement Some refer to sex and age and to dates of attending hospital, being treated and dying, and these may be accepted as statements of fact with little likelihood of error Others concern what the patient is reported to have said They are subject to all the inaccuracies of memory, selection and reporting Or the statements refer to the physical examination during life or after death, and to radiological, physical and chemical investigations they too may contain errors Finally there are the reported opinions of the interpretation of symptoms, signs and investigations, and on the disease category to which the patient was assigned If, therefore, hospital records are used to investigate the evolution, course and termination of a disease, the statements in them must be dealt with as reports of varying degrees of reliability, not as facts about the disease Inferences from them can be assumed to be facts only when the degree of reliability of the reports appears to justify it

The statement that a number of men with lung cancer attended a hospital during a particular period is only true if all did, in fact, have a lung cancer But there is frequently some doubt of the diagnosis Even the evidence of necropsy may not be conclusive and two examples of a wrong necropsy diagnosis have been reported by Smithers (1953) The statement should therefore refer not to 'men with lung cancer', but to 'men recorded as having lung cancer', unless there are demonstrably good reasons for assuming that the recorded disease was the disease from which the patient suffered.

Much of the investigation of disease from hospital records employs

. . . I became quite tired of the difficulty of attempting to explain the phenomena observed . . . and . . . gave up all further attempts at diagnosis.

Graves, R. J. (1848): *Clinical Lectures on the Practice of Medicine, Vol.* **2**, *p.* 75. *Dublin Reprinted by the New Sydenham Society, London,* 1884

Source of the Material

The material consists of 1,749 case records of patients thought to have lung cancer who were seen at the Brompton Hospital or the Royal Marsden Hospital during the years 1951 to 1955. A few patients may well have been missed, but none have been deliberately excluded. About one-third attended the Joint Consultation Clinic of the two hospitals The course of the illness has been followed in the majority from the out-patient records and from reports supplied by general practitioners and other hospitals In a small proportion no details of the after-history are available and the date of death has had to be obtained from the General Registry Office

The Diagnosis

All the patients were diagnosed as having a lung cancer. The diagnosis may not have been correct in all of them; but it seems likely that few were, in fact, misdiagnosed The case records have been reviewed and only those in which there appeared no reasonable doubt retained There was histological or cytological evidence of malignancy in 65 per cent (Table XXXII) Many of the 32 per cent in whom there was only clinical and radiographic evidence, with or without bronchoscopy reports, died with unmistakable metastases In the few who were last reported to be still alive and well, the evidence, though not conclusive, appeared sufficient to maintain the original diagnosis

The validity of the diagnosis was the same in the women as in the men There were, on the other hand, differences between different age groups The proportion without microscopic evidence of cancer rose from 34 per cent of patients under 40 years of age to 74 per cent of those 70 and over, thus reflecting

Table XXXII

Evidence of Malignancy in the Present Series

	Men		Women		Total	
Histological evidence						
Necropsy	62		10		72	
Resected specimen	349		34		383	
Biopsy—bronchial	426		46		472	
secondary	130		23		153	
Total		967		113		1,080
Cytological evidence only		45		9		54
Histological or cytological evidence		1,012		122		1,134 (65%)
Other evidence						
Necropsy	42		9		51	
Thoracotomy	6		—		6	
Clinical and radiographic with or without bronchoscopic	492		66		558	
Total		540		75		615 (35%)
Total		1,552		197		1,749 (100%)

comparisons. It may, for instance, be asserted that ten times more men than women with lung cancer attended the hospital. This statement is only true if there is reason to believe that the diagnosis was no more likely to be wrong in one sex than the other—an assertion that may well be correct, but which should not be assumed without consideration. In many comparisons it is, indeed, justifiable to assume that the reliability of the information is the same on the two sides of the comparison. Thus, although the record of the first symptom of the disease may be—and usually is—grossly inaccurate, the record of a particular symptom can be validly used in comparisons concerned, for instance, with the site of the tumour; for there seems no reason to believe that a symptom will be more correctly called the first in patients with a cancer of one lobe than in those with a cancer of another.

The inherent inaccuracy of hospital records need not, therefore, invalidate all inferences from them. But it is essential that every inference from the records should be held valid only for what is recorded until it has been shown reasonably probable that the record is a statement of fact. Inferences from comparisons are also unacceptable as facts about the disease unless it is reasonably probable that the degrees of reliability of the statements in the records are independent of the nature of the characteristics being compared.

Selection

It is impossible to draw general conclusions on many aspects of lung cancer from the records of a single hospital or group of hospitals. The relative incidence of the disease in men and women, for instance, can only be stated with reference to time and place and the population 'at risk'. Different figures may be obtained from necropsy records, death certificates and hospital admissions within the same locality; and the incidence may vary from place to place and from year to year. Moreover, the observed incidence from any source or combination of sources cannot be translated without reservation into the prevalence of the disease; for, except in small self-contained communities in special circumstances, it is unlikely that all instances of the disease will be correctly recorded.

Comparison of one set of figures with others obtained from different environments at different times by different observers may be fruitless. The reported frequency of resections at one hospital, for instance, can be compared with that at another; but the result merely expresses the similarities and differences in the practice of different hospitals; it does not necessarily produce facts about the disease itself. There is no 'resection rate' for lung cancer, only a number of rates for specified categories of patients in particular hospitals at particular times. Similarly, the frequency with which the various symptoms and signs occur in the disease cannot be estimated by collecting together all the published reports of the frequency with which they are recorded. Such compilation would signify little concerning the disease itself.

In the following account of the course of lung cancer, the published statistical data have been used only when their inclusion appeared justified by the nature of the evidence and the apparent validity of the comparisons.

Source of the Material

The material consists of 1,749 case records of patients thought to have lung cancer who were seen at the Brompton Hospital or the Royal Marsden Hospital during the years 1951 to 1955. A few patients may well have been missed; but none have been deliberately excluded. About one-third attended the Joint Consultation Clinic of the two hospitals. The course of the illness has been followed in the majority from the out-patient records and from reports supplied by general practitioners and other hospitals. In a small proportion no details of the after-history are available and the date of death has had to be obtained from the General Registry Office.

The Diagnosis

All the patients were diagnosed as having a lung cancer. The diagnosis may not have been correct in all of them; but it seems likely that few were, in fact, misdiagnosed. The case records have been reviewed and only those in which there appeared no reasonable doubt retained. There was histological or cytological evidence of malignancy in 65 per cent (Table XXXII). Many of the 32 per cent in whom there was only clinical and radiographic evidence, with or without bronchoscopy reports, died with unmistakable metastases. In the few who were last reported to be still alive and well, the evidence, though not conclusive, appeared sufficient to maintain the original diagnosis.

The validity of the diagnosis was the same in the women as in the men. There were, on the other hand, differences between different age groups. The proportion without microscopic evidence of cancer rose from 34 per cent of patients under 40 years of age to 74 per cent of those 70 and over, thus reflecting

Table XXXII

Evidence of Malignancy in the Present Series

	Men		*Women*		*Total*	
Histological evidence						
Necropsy	62		10		72	
Resected specimen	349		34		383	
Biopsy—bronchial	426		46		472	
secondary	130		23		153	
Total		967		113		1,080
Cytological evidence only		45		9		54
Histological or cytological evidence		1,012		122		1,134 (65%)
Other evidence						
Necropsy	42		9		51	
Thoracotomy	6		–		6	
Clinical and radiographic with or without bronchoscopic	492		66		558	
Total		540		75		615 (35%)
Total		1,552		197		1,749 (100%)

the well known tendency for older people, in whom surgical treatment is less applicable, to be less searchingly investigated.

The Series as a Sample of the Population

Almost all the patients lived in Greater London and the majority in the south-west part of it A few came from the provinces and a handful from abroad This group of patients is, therefore, a sample drawn mainly from the population of London. But they are not necessarily a representative sample of all the instances of lung cancer in that region. They were selected in many ways, depending on such factors as the nearness of their homes to the hospital, the routine practice of their general practitioners, and the likely need of radiotherapy or surgery.

The actual prevalence of lung cancer in a population could only be known if all instances of the diseases were accurately diagnosed and recorded either during life or after death. This probably never happens. The sample of the lung cancer population that is obtained from death certificates may be the best estimate that it is possible to get. It is at present the only valid working estimate. The characteristics of a collected series of cases should, therefore, be compared with those of the recorded deaths during the same period and in the same locality in order to estimate how the series differs from the real population of lung cancer patients

Age and Sex

The age and sex structure has been compared with that of patients recorded as having died with lung cancer in the County of London in the years 1951 to 1955. There were 8,504 recorded deaths in this period (London County Council 1956, County Medical Officer, personal communication). The number seen at the Brompton and Royal Marsden Hospitals is 21 per cent of the number of recorded deaths, but the proportion is not the same in women as in men or in the different age groups within each sex (Table XXXIII, Fig 42) There were

TABLE XXXIII

The Patients seen at the Brompton and Royal Marsden Hospitals (BH/RMH) during 1951–55 Compared in Age Groups with Recorded Deaths from Lung Cancer in the County of London (L C C.) during the same period

		Age (years)					Total
		under 45	45–54	55–64	65–74	75 or more	
MEN	BH/RMH	101	431	651	331	36	1,550*
	L C C	354	1,322	2,364	2,275	718	7,033
WOMEN	BH/RMH	16	54	68	51	8	197
	L C C	88	232	393	441	317	1,471
BH/RMH as per cent of L C C	Men	29%	33%	28%	14%	5%	22%
	Women	18%	23%	17%	12%	3%	13%

* In 2 of the 1,552 men the age was not recorded

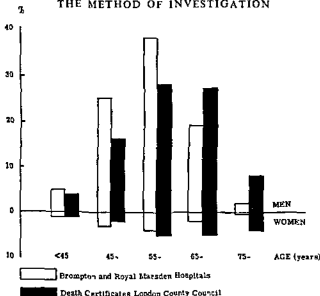


Fig 42
The age and sex distribution of a group of patients seen at two special hospitals (1,749) compared with that of the recorded deaths in the same period in the area from which the patients were drawn (8,504)

1,471 deaths in women and 197 women were seen at the hospitals, this being 13 per cent of the deaths, the corresponding proportion in men was 22 per cent The proportion was smallest in both sexes among those over the age of 65 and highest in those aged 45–54 years If the patients had been divided into age and sex groups in the same proportions as were those who died in the area during the period, there would have been 302 women and 1,445 men instead of 197 women and 1,552 men—differences of 105 (Table XXXIV) It appears

TABLE XXXIV

The Observed Age Distribution of the 1,749 Patients in the Brompton and Royal Marsden Hospitals Series Compared with the Distribution Expected if the Cases were Distributed Between the Age Groups in the Same Proportions as the Recorded Deaths from Lung Cancer in the County of London During the Same Period

		Age (years)					*Total*
		under 45	45–54	55–64	65–74	*75 or more*	
MEN	*Observed*	101	431	651	331	36	1,550*
	Expected	77	270	486	465	147	1,445
	Difference	+24	+161	+165	−134	−111	+105
WOMEN	*Observed*	16	54	68	51	8	197
	Expected	18	47	81	91	65	302
	Difference	−2	−7	−13	−40	−57	−105

* In 2 of the 1,552 men the age was not recorded

that there was a deficiency of persons over the age of 65 in the hospital series in comparison with the recorded deaths in the County of London—the deficiency being 40 per cent and 62 per cent of the expected numbers in men and women respectively.

In the group of patients in hospital reported by Doll and Hill (1952) there were also relatively few between the ages of 65 and 74—204 (14 per cent) of 1,465. During the same period—1948 to 1952—31 per cent of the deat[hs] certified to have been caused by lung cancer in the County of London were i[n] this age group (Table XXXV) In both these two large hospitals series, therefore, there was a discrepancy in the older age groups compared with the pattern

TABLE XXXV

Proportions of Older Patients in Two Clinical and Two Necropsy Series Compared with Recorded Deaths in the County of London During the Same Periods

	Period	*Proportion of older patients*	*Proportion in the same age group among recorded deaths in County of London during the same period*
CLINICAL			
Present series Special hospitals	1951–55	24% aged 65 or more	46%
Doll and Hill (1952) General and special hospitals	1948–52	14% aged 65–74	31%
NECROPSY			
Galluzzi and Payne (1955) Teaching and non-teaching hospitals	1948–52	17% aged 70 or more	12% aged 75 or more
Bryson and Spencer (1951) Non-teaching hospitals	1936–47	approximately 7% aged 75 or more	9%

shown by death certificates. The accuracy of the death certificate diagnosis may be roughly checked by comparing the age distribution of death certificate records with that of necropsy series, in which the diagnosis is beyond reasonable doubt The age pattern of 741 patients in the necropsy series of Galluzzi and Payne (1955) from teaching and non-teaching hospitals is in fact similar to that obtained from death certificates in London during the same period: 17 per cent of the necropsy series were in the age group of 70 years or more and 12 per cent of the death certificates were of patients aged 75 or more; 38 per cent of the necropsy series were between 60 and 69 years old compared with 31 per cent of the death certificates between ages 65 and 74. A series of 866 necropsies on patients in non-teaching London hospitals between 1936 and 1947 was reported by Bryson and Spencer (1951). Their paper gives a histogram of the age distribution but not the figures themselves It appears from the histogram that approximately 7 per cent were 75 years old or more and 26 per cent between 65 and 74 During the same period the proportions in these two age groups certified dead from lung cancer in the County of London were 9 per cent and 27 per cent respectively These two comparisons may suggest,

therefore, that the death certificate diagnoses in old people are not grossly inaccurate.

As well as there being too few old patients in the Brompton and Royal Marsden Hospitals series, there appear to be too few women The male/female ratio was 7·9 to 1, compared with 4 8 to 1 from death certificates in the same period; and the ratio was higher in each age group. As in the case of age distribution, the two major necropsy reports in this country, both from the London area, give male/female ratios closer to those of death certificates (Galluzzi and Payne (1955)—4·7 to 1 compared with 4·9 to 1; Bryson and Spencer (1951)—6 to 1 compared with 4·3 to 1)

There may, of course, be differences in the way the young and old and men and women are selected for admission to different hospitals The patients in the necropsy series of Bryson and Spencer had died in hospitals under the charge of the London County Council These hospitals accepted any type of patient, irrespective of age or the severity of the illness Those in the series of Galluzzi and Payne were in eight hospitals, some of which were teaching hospitals, where the intake may have been more selective, but there was no *consistent difference in sex ratio between the teaching and non-teaching* hospitals The highest sex ratios have been found among groups of patients reported from thoracic surgical clinics or special hospitals (for example, Ochsner, De Camp, De Bakey and Ray (1952)—9 to 1, Mason (1949)—9 to 1, Bignall and Moon (1955)—10 to 1; Sellors (1956)—10 to 1, Doll and Hill (1952)—12 6 to 1) In a large series from several hospitals in Birmingham the ratio for all patients was 7 to 1, but among those treated surgically it was 15 to 1 (United Birmingham Hospitals 1954) and in the present series the ratio among those who had a lung resection was 10·6 to 1, compared with the ratio in the whole series of 7·9 to 1

It seems that a higher proportion of men than women are admitted to general hospitals, attend special hospitals and thoracic surgical clinics or are operated on There may be many reasons As lung cancer is still rare in women it may be more frequently misdiagnosed until it is too late for reference to a special centre to be thought necessary The illness may have a more insidious beginning, making early diagnosis more difficult and thoracotomy less likely. Women may be less willing to come to hospital because of their family and household ties But none of these reasons is convincing Nor could they together explain the apparent paradox that, although fewer women appear to attend hospital, the published necropsy reports from hospitals show a sex ratio similar to that among certified deaths

Histological Type

In the previous section death certificates were taken as providing a reasonably close estimate of the real population as regards age and sex, but they do not provide any useful indication of the pattern of histological types In all but necropsy and surgical series there is likely to be a large proportion of patients without histological reports It cannot validly be assumed that the distribution of histological types among those in whom the type was unknown

is the same as that among the known. More with rapidly metastasizing tumours are likely to be among the 'unknowns' so that the apparent proportion of undifferentiated tumours in the series is too low. A surgical group is, of course, highly selected in favour of squamous tumours. Necropsy series may be slightly biased towards tumours causing rapid death, and they are unlikely in practice to be completely representative of the whole lung cancer population; but they [illegible]

patterns [illegible] More-over, the proportions of the different types will be influenced by the sex ratio of the group, the country of origin of the report and the period during which the cases were collected The reported frequency of squamous tumours in necropsy material has, for example, varied between 18 per cent to 24 per cent (Bryson and Spencer 1951; Jakobsen 1953; Galluzzi and Payne 1955; Walter and Pryce 1955*a*); around 30 per cent (Barnard 1938; Christiansen 1953); 40 to 45 per cent (Beeler and Irey 1950; Earle 1954); and 60 per cent (Fried 1938).

The necropsy series of Galluzzi and Payne (1955) concerned patients in the London area between 1948 and 1952 and is, therefore, suitable for comparison with the Brompton and Royal Marsden Hospitals clinical series (Table XXXVI) * If the necropsy figures can be regarded as closely approximating to the actual distribution of histological types, the present series appears

TABLE XXXVI

The Proportions of the Three Main Histological Types at Different Ages in the Present Series (Clinical) and the Necropsy Series of Galluzzi and Payne (personal communication)

Histological type	*Series*	*Proportion (per cent) of those with known histological type within the age group (years)*					
		under 40	40–49	50–59	60–69	70 *or more*	*All ages*
SQUAMOUS	*Clinical*	31	46	47	49	52	47
	Necropsy	28	15	20	29	23	24
UNDIFFERENTIATED	*Clinical*	55	49	46	45	46	46
	Necropsy	59	71	66	61	60	63
ADENOCARCINOMA	*Clinical*	14	5	7	6	2	7
	Necropsy	14	14	13	10	17	13
Total with known type	*Clinical*	29 (66%)	152 (64%)	442 (65%)	356 (56%)	44 (26%)	1,023 (59%)
	Necropsy	29 (100%)	86 (100%)	215 (100%)	285 (100%)	124 (100%)	739 (100%)
Total in series	*Clinical*	44 (100%)	238 (100%)	680 (100%)	618 (100%)	167 (100%)	1,747† (100%)
	Necropsy	29 (100%)	86 (100%)	215 (100%)	285 (100%)	124 (100%)	739 (100%)

† In 2 of the 1,749 patients the age was not recorded

* The figures on which this and subsequent Tables are based appear in Appendix II

deficient in undifferentiated tumours—46 per cent of those with recorded type compared with 63 per cent. Only in the small groups of patients under 40 years old are the two series similar. The large clinical series of Doll and Hill (1952) also contains a low proportion with undifferentiated cancers

Conclusions

Hospital series of patients with lung cancer differ from the real population with the disease in the age and sex structure and in the pattern of histological types. They appear to contain too few women and old people and too few with the more malignant tumours. The picture obtained from hospital clinical reports is, therefore, not a true representation of the course of the disease. It may present it in too favourable a light, with too great a prospect of radical treatment and cure.

CHAPTER XIV

THE SITE OF THE TUMOUR

J. R. BIGNALL

IT is commonly stated that lung cancer occurs more frequently in the right than the left lung. Walsh, in 1860, wrote that 'primary cancer affects a well-marked preference for the right, scarcely ever involving both organs'; and Adler, in his monograph published in 1912, found a preponderance of 'carcinomas' in the right lung and of 'sarcomas' in the left. He stated that 'comparison of these figures shows results so inconstant and differences so slight that it would not be wise to build any theories thereon'.

Ochsner and De Bakey (1942) collected 4,732 records of necropsies from the literature and found among them 58 per cent with cancer of the right lung and 42 per cent of the left; but in the reports of Bryson and Spencer (1951) and Rosenblatt and Lisa (1956) the tumours are almost equally divided between [illegible] reported by [illegible]

right predominated (Galluzzi and Payne, personal communication) The distribution among resected specimens is probably considerably influenced by selection. Here too there is disagreement. The series from the Mayo Clinic (Carlisle, McDonald and Harrington 1951; McBurney, McDonald and Clagett 1951; Patton, McDonald and Moersch 1951*a*, 1951*b*) and those of Ochsner, De Camp, De Bakey and Ray (1952) and Baldry (1952) contain more right- than left-sided cancers; but in those of Borrie (1955) and Nohl (1956) there were more from the left than the right lung. In the present clinical series there were 54 per cent with tumours in the right lung and 46 per cent in the left

There is considerably more variation in the recorded frequency of lobar involvement. This is not surprising, for, even with careful examination of the specimens at necropsy or after resection, it may be impossible to discover where the tumour originated. When the series includes a high proportion with only radiographic and bronchoscopic evidence, the recorded site of the tumour is likely to be even more inaccurate. In the necropsy series of Galluzzi and Payne there were 41 per cent recorded as being in the upper lobes, with proportions varying between the hospitals from 30 per cent to 49 per cent; there were 30 per cent in the lower lobes with a range of 21 per cent to 38 per cent; and 25 per cent in the main bronchi with a range of 14 per cent to 40 per cent. In six published series based on necropsies the proportion of upper lobe tumours varied from 19 per cent to 50 per cent, lower lobe from 17 per cent to 35 per cent and main bronchus from 27 per cent to 50 per cent (Simpson 1929; Willis 1948; Bryson and Spencer 1951; Stern 1954; Galluzzi and

Payne 1955; Rosenblatt and Lisa 1956). It is obviously impossible to state the frequency of involvement of the different bronchi in the whole population of lung cancers even from necropsy studies, where selection is likely to have had little effect on the composition of the sample in respect of the situation of the tumour.

It seems likely, however, that more cancers occur in the upper than the lower lobes. In the two large series of Bryson and Spencer (1951) and Galluzzi and Payne (personal communication) there were 33 per cent and 41 per cent respectively in the upper lobes compared with 24 per cent and 30 per cent in the lower (Table XXXVII). It has been suggested that tuberculous lesions of

TABLE XXXVII

The Site of the Tumours in this Series (BH/RMH) and in Three Necropsy Series

Series	*Proportion (per cent) at site*			*Total cases*
	Upper lobes	*Lower lobes*	*Main bronchus*	
BH/RMH	51	28	19	1,415*
NECROPSY REPORTS				
Bryson and Spencer (1951)	33	24	34	866
Galluzzi and Payne (*personal communication*)	41	30	26	741
Rosenblatt and Lisa (1956)	50	19	27	206

* In 334 of the 1,749 cases the lobar site of the tumour was not recorded

the lungs and bronchi may increase the susceptibility of the mucosa to inhaled carcinogenic substances (see p. 98). Chronic tuberculosis occurs more commonly in the upper lobes; and the observed predominance of upper lobe tumours appears to support the hypothesis Moreover, in women, who have been less exposed to inhaled carcinogens, upper lobe cancers are less frequent than in men. It seems likely, however, that there are other factors that affect the situation of the tumour; for adenocarcinomas may also be commonest in the upper lobes, although they are probably unrelated or less closely related to inhaled carcinogens.

In the report of Galluzzi and Payne there were more right- than left-sided lesions at all three major sites, but in those of Rosenblatt and Lisa (1956) and Bryson and Spencer (1951) there was no consistent preponderance of right-sided cancers

Relation to Histological Type

In both the present series and the necropsy series of Galluzzi and Payne there were almost the same proportions of squamous and undifferentiated tumours in the upper and lower lobes as in the main bronchi (Table XXXVIII). The proportion of undifferentiated tumours was higher among middle lobe

cancers; however, the numbers of tumours in this lobe were small (30 and 23 respectively) and, as there is such scope for inaccuracy in assessing the site of a cancer, it should not be assumed that tumours of the middle lobe are more frequently of the undifferentiated variety.

TABLE XXXVIII

The Proportion of Squamous and Undifferentiated Tumours at Different Sites in the Present Series (Clinical) and a Series Reported by Galluzzi and Payne (Necropsy)

	Total cases	*Proportion (per cent) of all tumours in*					
		Right lung	*Left lung*	*Upper lobes*	*Lower lobes*	*Main bronchi*	*Middle lobe*
SQUAMOUS							
Clinical series	485	49	45	47	51	52	(33)
Necropsy series	176	23	27	26	21	25	(13)
UNDIFFERENTIATED							
Clinical series	470	46	45	44	44	45	(63)
Necropsy series	503	70	74	66	72	69	(78)

Percentages in brackets are based on less than 100 cases.

Adenocarcinomas form a much smaller proportion of the total. Here, too, the differences between the sites are small (Table XXXIX); but in the present series, a necropsy series and two surgical groups there was a slightly larger proportion of adenocarcinomas in the upper than the lower lobes and a smaller proportion in the main bronchi. Walter and Pryce (1955*b*) found no adenocarcinomas of the main bronchi in their study of 207 resected specimens, all

TABLE XXXIX

The Proportions of Adenocarcinomas at Different Sites in the Present Series a Necropsy Series and Two Surgical Series

	Total cases	*Proportion (per cent) of all tumours in*					
		Right lung	*Left lung*	*Upper lobes*	*Lower lobes*	*Main bronchi*	*Middle lobe*
Present series	68	4	10	9	6	3	(3)
Necropsy series *Galluzzi and Payne (personal communication)*	50	7	8	8	7	5	(10)
Surgical series							
Bignall and Moon (1955)	60	15	12	15	11	0	0
Patten, McDonald and Moersch (1951a)	40	13	13	18	13	5	(12)

Percentages in brackets are based on less than 100 cases

the tumours placed in this category being judged 'peripheral'. In the Mayo Clinic series 65 per cent of adenocarcinomas were reported 'peripheral' and in a group of 421 reported by Ochsner, Ray and Acree (1954) there were 41 per cent. The recorded proportions of adenocarcinomas and peripheral tumours will, of course, depend on the definitions used as well as on the source of the material (see p. 123). For example, the proportion of peripheral lesions in necropsy material has been reported as 10 per cent (Rosenblatt and Lisa 1956), 7 per cent (Willis 1948; Stern 1954), and as low as 3 per cent (Bryson and Spencer 1951); while in surgical specimens Walter and Pryce reported 53 per cent, and Ochsner, Ray and Acree (1954) 33 per cent. Walter and Pryce (1955*a*), using the same criteria for histological classification, found 15 per cent of adenocarcinomas in their resected specimens and nearly twice as many (28 per cent) in their necropsy specimens

It appears likely that adenocarcinomas are, in fact, less common in the larger bronchi; but the evidence that they are more common in one lobe than another is not yet convincing.

Relation to Sex and Age

The tumour was in the right lung in a higher proportion of women (58 per cent) than men (53 per cent) (Table XL) The difference is small, but it is

TABLE XL

The Recorded Site of the Tumour Related to the Sex and Age of the Patients and the Histological Type

	Proportion (per cent) with tumours in					
	Right lung	*Left lung*	*Upper lobes*	*Lower lobes*	*Main bronchi*	*Middle lobe*
Men	53	47	52	28	18	2
Women	58	42	42	29	27	2
Age (years)						
Under 40	(50)	(50)	(44)	(18)	(24)	(14)
40–49	59	41	48	30	18	3
50–59	57	43	51	27	19	2
60–69	50	50	50	30	18	2
70 or more	48	52	59	24	16	3
Histological Type						
Squamous	58	42	44	32	22	2
Undifferentiated	56	44	45	30	20	5
Adenocarcinoma	(37)	(63)	(62)	(27)	(10)	(1)
Not known	15	49	59	21	15	5

Percentages in brackets are based on less than 100 cases.

found, though to a less extent, in the necropsy series of Galluzzi and Pa (58 per cent of 128 and 55 per cent of 608). In both series the male/fem ratio was not only lower in the right than the left lung, but also in the ma bronchus than the lower lobes and the lower lobes than the upper lob (Table XLI). The tumours in women appear, therefore, to be relativel

TABLE XLI

The Male/Female Ratio at Different Sites in the Present Series (BH/RMH) and a Necropsy Series (Galluzzi and Payne, personal communication)

Site		*BH/RMH*		*Necropsy series*	
		Total	*Male/Female*	*Total*	*Male/Female*
Upper lobes	*R*	377	8·7 : 1	157	8·2 : 1
	L	343	17·0 : 1	142	6·4 : 1
	Total	720	11·4 : 1	299	7·3 : 1
Lower lobes	*R*	215	9·2 : 1	123	4·4 : 1
	L	179	8·4 : 1	97	6·9 : 1
	Total	394	8·9 : 1	220	5·2 : 1
Main bronchus	*R*	137	5·8 : 1	98	4·7 : 1
	L	126	6·4 : 1	90	5·0 : 1
	Total	263	6·1 : 1	188	4·8 : 1
Right middle lobe		38	18·0 : 1	23	3·8 : 1
Right lung		932	8·2 : 1	405	5·5 : 1
Left lung		797	9·9 . 1	331	6·2 . 1

commoner in the main bronchi and lower lobes, although adenocarcinomas, which form a higher proportion of all cancers in women than in men, are probably less common at these sites. The reason for this is unknown.

In the necropsy series there was no simple relationship between the age of the patient and the site of the tumour. The proportion of left lung tumours was highest in the patients aged 60–69 (Table XLII). The proportion of tumours appeared to be caused almost entirely by the [illegible] (50 per cent) [illegible] s. The findings ma[illegible] but a similar increa[illegible] group appears in the clinical series also ([illegible]). In this series, however, the proportion of left-sided lesions is even higher in those aged 70 or more; but in this small group the number in whom the lobar site was not known is large and the observed pattern is consequently less reliable.

TABLE XLII

The Site of the Tumour in a Necropsy Series Related to the Ages of the Patients (Galluzzi and Payne, personal communication)

Site		Total	Age (years)				
			under 50	50–59	60–69	70 or more	Not known
Upper lobe	R	157	28	53	50	26	—
	L	142	21	40	63	17	1
	Both	299	49 (43%)	93 (44%)	113 (39%)	43 (35%)	1
Lower lobe	R	123	16	38	42	26	1
	L	97	18	24	37	18	—
	Both	220	34 (39%)	62 (29%)	79 (28%)	44 (36%)	1
Main bronchus	R	98	15	25	41	17	—
	L	90	11	23	40	16	—
	Both	188	26 (23%)	48 (23%)	81 (29%)	33 (27%)	—
Right middle lobe		23	5 (4%)	9 (4%)	6 (2%)	3 (2%)	—
Lobe unknown	R	4	—	—	4	—	—
	L	2	1	1	—	—	—
Total	Right lung	405	64 (56%)	125 (59%)	143 (50%)	72 (59%)	1
	Left lung	331	51 (44%)	88 (41%)	140 (50%)	51 (41%)	1
Total		736	115 (100%)	213 (100%)	283 (100%)	123 (100%)	2

In summary, lung cancer occurs a little more commonly in the right lung than the left and in the upper than the lower lobes. Adenocarcinomas are less frequent in the main bronchi. Cancers appear to be slightly more common in the right lung in women than in men. There is no definite relation between the age of the patient and the site of the tumour.

CHAPTER XV

TREATMENT AND SURVIVAL

J. R. BIGNALL

THE surgical treatment and radiotherapy of lung cancer are fully discussed elsewhere (Chapters XXI and XXII). The following description of the experience of patients at the Brompton Hospital and Royal Marsden Hospital during a period of 5 years is presented merely to illustrate the pattern of the disease as it is seen at these hospitals The survival experience of the patients not treated surgically or by radiotherapy has also been used to investigate whether the age and sex of the patients and the histological type and site of the tumour influence the duration of survival.

TREATMENT

The great majority of the patients in this series who were treated by surgery or radiotherapy received the treatment at the Brompton or Royal Marsden Hospital under the care of the physicians, surgeons and radiotherapists. Radiotherapy was in most cases arranged after consultation in the Joint Consultation Clinic (see Chapter XXII). The treatment of the whole group of patients has therefore not been according to a single uniform policy; and the series combines the practice of many individuals.

Of the 1,749 patients, about three-quarters (77 per cent) did not have the primary tumour removed.

At the time the decision on treatment was made there was clinical, radiographic or bronchoscopic evidence of metastases in 37 per cent. In 7 per cent a thoracotomy was done but the tumour was too extensive to be removed either because of local node metastases or of invasion of adjacent structures; 5 per cent were grossly cachectic, although there were no manifest metastases; and 3 per cent had a pleural effusion presumed to be malignant or involvement of the chest wall. Thus, just over half the patients were not treated surgically because the condition was already too advanced.

In 8 per cent the situation of the primary precluded successful removal; a few refused investigation or thoracotomy and 4 per cent appeared to have insufficient respiratory reserve to tolerate removal of part of the lung In the remaining 11 per cent the contra-indications could not be so easily classified· some were too old to withstand a thoracic operation; others had severe cardiovascular or other diseases, in some there were a number of minor factors which, taken together, made operation inadvisable; and in a few no reason was recorded or apparent from the case history. One quarter, therefore, were not operated on for reasons unconnected with the stage of development of the disease.

Thoracotomy was done in a little over a quarter (29 per cent) of the patients. In about a quarter of these the condition was considered too advanced for the cancer to be resected. 396 (23 per cent) had either a lobectomy (104) or a pneumonectomy (292)

Treatment by radiotherapy alone was given to 574 patients. In the remaining 779—nearly half the entire group—it was considered that neither surgical treatment nor radiotherapy could help.

The pattern of treatment will, of course, vary with the composition of the group of patients and the practice of the physicians, surgeons and radiotherapists who look after them The pattern seen at these two special hospitals does not differ in any important respect from that reported previously. Thus, in the series from the United Birmingham Hospitals (1954) between 1936 and 1952 20 per cent of 4,103 patients had a thoracotomy and 12 per cent a resection. Radiotherapy was employed in 28 per cent and 52 per cent had neither treatment; 13 per cent survived a year and 5 per cent 2 years. Some other large series have come from thoracic surgical centres Ochsner, Ray and Acree (1954), for instance, had 32 per cent of resections with a five-year survival rate among 1,170 treated and untreated cases of 8 per cent

It is not known how many resections for lung cancer are carried out each year in the whole of this country or the proportion of resections within the whole lung cancer population Special hospitals and probably many general hospitals appear to see relatively few elderly patients and patients with more malignant tumours. It seems likely, therefore, that of all the lung cancers in the country less than a quarter are resected and more than half have neither surgical treatment nor radiotherapy.

SURVIVAL

The survival experience of the whole group is shown in Table XLIII and Figure 43. 1·6 per cent of the patients are at present untraced; following the usual practice, they are counted as having died. The five-year survival rate of the whole group from the time they first attended the hospitals was only 6 per cent; and all these patients had been treated surgically. This is a selected series. The resection rate among the whole population is probably much smaller than it was in this group. It seems reasonable to conclude that of every 1,000 who developed a lung cancer in Great Britain in 1951 not more than 40 were alive by the end of 1956 Gifford and Waddington (1957) have estimated that in the Liverpool area only about 6 per cent of all patients live for 2 years with the existing standards of diagnosis and treatment.

The survival rates of the treated patients shown in the Table refer to the [illegible]

TABLE XLIII

The Survival Rates from First Attendance at the Brompton or Royal Marsden Hospital

	At risk	*Died in period*	*Untraced*	*Alive at end of period*	*Survival rate (per cent)*
Resection					
1 year	396	141	4	251	63
2 years	310	159	2	149	48
3 years	227	137	3	87	38
4 years	139	94	1	44	32
5 years	63	43	—	20	(32)
Radiotherapy, 'Radical'					
1 year	168	93	—	75	45
2 years	141	120	—	21	15
3 years	112	103	—	9	8
4 years	68	65	—	3	(4)
5 years	38	38	—	0	(0)
Radiotherapy, 'Palliative'					
1 year	406	322	8	76	19
2 years	316	295	6	15	5
3 years	236	229	3	4	2
4 years	158	155	1	2	1
5 years	91	90	1	0	(0)
No Resection or Radiotherapy					
1 year	779	151	16	135	17
2 years	635	601	8	26	4
3 years	485	477	2	6	1
4 years	312	309	1	2	1
5 years	151	151	—	0	0
Total					
1 year	1,749	1,194	28	527	30
2 years	1,402	1,175	16	211	16
3 years	1,060	946	8	106	10
4 years	677	623	3	51	8
5 years	343	322	1	20	6

Percentages in brackets are based on less than 100 cases.
The highest proportion of untraced patients was 1·6 per cent.

were in good enough general condition to withstand such treatment: their survival rate is the next highest. Those treated by shorter courses of radiotherapy either had extrathoracic metastases—for which they were treated—or were in poor general condition: their survival rate is the lowest.

Effect of Certain Factors on the Survival of Patients Not Treated by Surgery or Radiotherapy

Although the course of the illness in a single patient not treated by a potentially curable procedure illustrates the natural history of the disease, the experience of a group of such patients is not necessarily an expression of it. If potentially curable treatments are used in some patients, those not treated form a selected group. Two such groups cannot be validly compared unless

such selection can reasonably be believed not to have biased one or the other in favour of survival. For example, a group of patients may have a high resection rate and a high proportion treated by radical radiotherapy because it contains a low proportion of rapidly advancing tumours; the 'untreated' from such a group probably consist largely of patients with these highly malignant cancers and their survival rates will be small. On the other hand

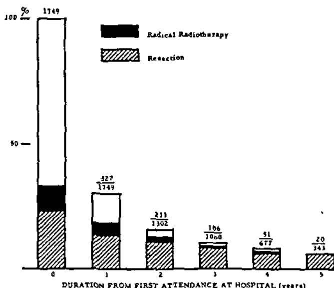


FIG 43

The survival rates of 1,749 patients from the time they were first seen at two special hospitals

the 'untreated' from a group with a low resection rate because of old age may contain a relatively high proportion of the slowly killing tumours; and the survival rate of the 'untreated' will be high. When survival rates of 'untreated' patients are compared therefore, the reasons for them being 'untreated' should also be considered.

Age—The survival rates appear to rise with increasing age (Table XLIV and Fig 45 p. 184). This may be an expression of the different reactions of old and young tissues to the malignant change; but it may also be partly produced by the decreasing proportion treated by resection and radiotherapy.

Sex—The survival rates among the women were little different from those in the men.

Duration of Symptoms before First Examination—The rates fell with increasing durations of illness but rose again in those with histories of 6 months or more. The proportions resected showed similar trends.

TABLE XLIV

The Proportion of Patients Not Treated by Resection or Radiotherapy who Died Within a Year of First Attending the Hospitals

	Total	*Survived 1 year (per cent)*
Men	679	18
Women	100	14
Age (years)		
Under 40	14	(7)
40–49	71	(7)
50–59	257	15
60–69	317	20
70 or more	119	21
Histological type		
Squamous	156	25
Undifferentiated	158	12
Adenocarcinoma	15	(0)
Unknown	450	17

	Total	*Survived 1 year (per cent)*
Symptoms for		
Under 1 month	68	(25)
1–2 months	236	17
3–5 months	168	12
6–11 months	138	21
12 or more months	65	(17)
No symptoms	18	(11)
Site		
Upper lobes	294	22
Lower lobes	146	25
Main bronchi	118	11
Right lung	397	16
Left lung	368	19

Percentages in brackets are based on less than 100 cases

Histological Type—Those known to have squamous cancers had higher survival rates than those with undifferentiated tumours. There were 15 with adenocarcinomas; none lived a year

Site—The lowest survival rates were found among those with main bronchus tumours, in whom there was also the lowest resection rate. The difference between the right and left lungs is small, but there is a similar difference in both upper and lower lobe groups, the rate being higher with tumours on the left side.

THE MANNER OF DYING

Little has been recorded of the pattern of the mode of death in patients with bronchial carcinoma. It is, indeed, difficult to discover and describe it. Ways of dying are not easily classified. There is a gradation of suffering between a sudden fatal haemoptysis or coronary thrombosis and a protracted illness with wasting, pain, dyspnoea, and lung suppuration. To measure suffering is impossible. A patient with cerebral metastases may well suffer less than one who, although having few outward signs of illness, knows that he will soon die. On the other hand, a paralysed patient with unclouded mind

may suffer more than one who wastes painlessly and dies quickly Harnett (1952) recorded some details of the mode of death in nearly 1,000 patients. In two-thirds the dominant feature was progressive wasting and dissolution of well-being; and one in five had gross pulmonary infection. The manner of dying has been studied in the first 283 deaths in the present series (Bignall 1955*a*). The information about the final stages of the illness had to be collected by inquiring from general practitioners and from hospitals, since only a few patients were personally observed in the last stages of the illness. The inquiries produced adequate data for the very broad classification adopted in only 128 of the 283 who are known to have died. Only a very incomplete picture can be obtained; and no firm conclusions about the frequency of the modes of death can be drawn from it.

Of the 25 who died after resection 10 had clinically manifest cerebral metastases; 9 slowly got thinner and weaker but in none did intense pain dominate the illness. One also had superior vena caval obstruction, another severe dysphagia and a third extensive ulcerating skin metastases; 4 died within a few weeks after operation and their deaths can reasonably be attributed to it. Two were thought to have had a coronary thrombosis

Only 2 of the 18 who died after radical radiotherapy had signs of cerebral metastases; 15 slowly deteriorated, and severe pain was reported in 2 Another with severe dysphagia attempted suicide, and 1 had a secondary deposit in the spine with paralysed legs. 1 patient died after a large haemoptysis

Of the 85 who had symptomatic treatment only there were 14 (16 per cent) with signs of cerebral metastases 65 (77 per cent) deteriorated slowly, and in 12 of these intense pain dominated the illness. 11 died with symptoms of superior vena caval obstruction, although 8 had previously been treated for this by radiotherapy; 5 had severe dysphagia; 2 became addicted to morphia; 6 (7 per cent) died suddenly—2 from a presumed coronary thrombosis and 4 after large haemoptyses

It seems likely that more than two-thirds of those who are treated surgically die slowly with increasing weakness and wasting but without signs of cerebral metastases. In only a few is the pain from the primary tumour or from metastases sufficiently intense to dominate the clinical picture, although it is rare for there to be no pain at all throughout the illness. Probably about 1 in 7 have manifest cerebral metastases. Sudden death before cachexia has become advanced is uncommon, and fatal haemoptysis probably occurs in only about 1 in 20 Such distressing conditions as dysphagia, ulcerating skin metastases, and choking from tracheal narrowing are rare; but superior vena caval obstruction with the frightening sensations of constriction and congestion and the swollen, cyanosed neck and face occurs in about 1 in every 10 patients

CHAPTER XVI

THE EFFECT OF HISTOLOGICAL TYPE

J. R. BIGNALL

THE histological appearances reflect the capability of the neoplasm for growth and spread, though they are not a complete statement of it. Some tumours classed as 'squamous' may kill quickly and others called 'undifferentiated' slowly. A more complete expression of malignancy would be given by statements of both the cellular pattern and the known extent of the primary lesion and its secondaries.

The histological category alone, however, does provide a simple practical indicator; and it is not surprising that many features of the course of the disease are related to it.

There appears to be little difference between the histological types in the way in which the illness begins. Harnett (1952) found that haemoptysis was more frequently reported as the first symptom with squamous tumours than with others. In the present series 16 per cent with squamous cancers began with haemoptysis, compared with 12 per cent with undifferentiated and 9 per cent with adenocarcinomas. The differences are quite small; and if haemoptysis is indeed more frequent with squamous tumours it is probably merely an expression of their slower evolution and more frequent occurrence in the larger bronchi.

It has been said that patients with undifferentiated tumours have shorter histories of illness before coming to hospital (King 1938; Björk 1947; Bryson and Spencer 1951; Moersch and McDonald 1953). A rapidly evolving tumour might be expected to bring the patient for advice earlier than a slowly growing one. There are, however, many other factors affecting the recorded duration of illness; and in this series there were only trivial differences between the squamous and undifferentiated groups. 9 per cent of those with squamous type tumours were not seen until they had had symptoms for a year or longer; but so were 10 per cent of those with undifferentiated lesions. The length of the illness is of little help in assessing the histological type of tumour.

Those with undifferentiated tumours are certainly more likely to have clinically or radiographically manifest metastases when first examined. Metastases were detected in 33 per cent of all our cases (Table XLV). In a large proportion of these no histological diagnosis was made, many of the patients being too ill to justify further investigation. It is likely that this group contained a larger proportion with highly malignant tumours than the group with histological diagnoses. The observed proportion of undifferentiated tumours among patients with metastases might, therefore, have been higher if all had been investigated. As it was, only 28 per cent of those known to have

undifferentiated tumours had metastases, compared with 18 per cent of those known to have squamous cancers—a relatively small difference. The disease in patients with undifferentiated tumours may be in a more advanced stage of its evolution, even though the length of history suggests that it is not in a later stage.

A patient with an undifferentiated cancer is less likely to be acceptable for surgical treatment. Of the 470 known to have undifferentiated tumours,

TABLE XLV

Clinical and Radiographic Evidence of Metastases at First Examination Related to the Histological Type of the Tumour

Metastases	*Proportion (per cent) within each type*				*Total cases*
	Squamous	*Undifferentiated*	*Adenocarcinoma*	*Not known*	
Regional only	14%	19%	7%	28%	376 (22%)
Distant with or without regional	4%	9%	16%	17%	201 (11%)
None	82%	72%	71%	55%	1,172 (67%)
Total cases	485	470	69	725	1,749 (100%)

43 per cent had a thoracotomy and 76 per cent of these a resection; a slightly higher proportion (47 per cent) of those with squamous tumours had a thoracotomy, and a higher proportion (87 per cent) of them had the tumour removed. On the other hand, because relatively fewer with undifferentiated tumours are surgically treated, more receive radiotherapy

It is well known that undifferentiated tumours kill quicker than squamous ones (Buchberg, Lubliner and Rubin 1951; Harnett 1952; United Birmingham Hospitals 1954; Bignall 1955*b*) Of 156 patients with squamous tumours in our series who were not treated by surgery or radiotherapy, 25 per cent lived a year after diagnosis compared with 12 per cent of the 158 with undifferentiated tumours.

ADENOCARCINOMAS

The adenocarcinomas are an interesting group. Because they are relatively [illegible]

main types, these variations may have more disturbing effects. Certainly the recorded frequency of adenocarcinomas varies widely even in the same country during approximately the same period. Thus, in the necropsy series of Bryson and Spencer (1951) it was almost 5 per cent and in that of Galluzzi and Payne (1955) 13 per cent; but in the group reported by Walter and Pryce (1955*a*) it was 28 per cent The proportion varied from 2 per cent to 23 per cent among a

group of 8 hospitals even when only one sex (men) was considered (Galluzzi and Payne, personal communicat...

10 per c... 1954; 9 per cent—Mason 1954;
19 per ... Clagett, Moersch and Gage 1955;
Rubin 1951). In the present series there were 69 (7 per cent) ...

than ...

men; Galluzzi and Payne 1955—17 per cent and 12 per cent; Doll and Hill 1952—13 per cent and 4 per cent; present series—14 per cent and 6 per cent).

There is a suggestion that adenocarcinomas may be relatively more frequent in younger people. In the series of hospital patients reported by Doll and Hill (1952) the proportion known to have adenocarcinomas fell from 8 per cent of those less than 45 years old to 2 per cent of those between 65 and 74. In the present series it was 14 per cent among patients less than 40 and 6 per cent among those aged 60 to 69. In both series, however, there were more patients in the older age groups without histological diagnosis and valid comparison of the pattern of histological types between the age groups is impossible. Moreover, in the necropsy series of Galluzzi and Payne (1955, personal communication) covering approximately the same period and drawn from a similar population as was the series of Doll and Hill, the proportion of adenocarcinomas (13 per cent) was no higher in those less than 40 than in the age groups over 40.

The behaviour of the adenocarcinomas differs from that of the other types. The tumours generally begin more peripherally than the squamous carcinomas (see p. 164); but there appears to be little difference in the manner in which they become manifest, except that a higher proportion are discovered by routine chest radiography in patients without symptoms—in this series 9 per cent compared with 4 per cent of each of the other groups. When symptoms do occur the illness has been reported to be slightly more prolonged before the patient comes to hospital (Björk 1947; Moersch and McDonald 1953). This is confirmed in our investigation, for only 32 per cent of the 59 with adenocarcinomas in whom the duration of symptoms was known had histories of less than 3 months, whereas the proportions were 46 per cent and 44 per cent in those with undifferentiated and squamous tumours respectively.

From the experience of the patients with adenocarcinomas in this series it appears that distant metastases with or without regional metastases are more frequently discovered at the first examination than regional metastases alone (Table XLV). In the case of squamous and undifferentiated tumours the proportion with only regional metastases is the higher. Studies of necropsy material suggest that the squamous tumours tend more commonly to spread locally and to regional lymph nodes rather than to distant organs; and that the adenocarcinomas behave like the undifferentiated group, spreading about as frequently distantly as locally (Koletsky 1938; Klotz 1938; Gebauer 1941). The proportion of patients with metastases at any site is also higher in those

with adenocarcinomas than with squamous cancers (Galluzzi and Payne 1955 and 1956) and may be as high as or higher than those with undifferentiated tumours (Engelman and McNamara 1942; Bryson and Spencer 1951). There have been few studies of the frequency and extent of involvement of blood vessels by the primary tumour; but in the report of Ballantyne, Clagett and McDonald (1957) on 59 surgically removed specimens, all 6 adenocarcinomas showed vascular invasion, as did all 19 'large' and 'small cell' types but only 27 of 34 squamous tumours. It seems that the adenocarcinoma, although histologically a 'differentiated' tumour, is in fact, a highly malignant one (see also p. 133).

It is not known what proportion of the total of all adenocarcinomas can be resected. In this series, as in others (United Birmingham Hospitals 1954, Kirklin, McDonald, Clagett, Moersch and Gage 1955) the proportion seems to be higher than with the undifferentiated tumours; but unless all tumours in the population studied are examined histologically it cannot be assumed that the observed proportion is the real one. Adenocarcinomas, because of their situation, are less commonly diagnosed by bronchial biopsy; and a series of histologically confirmed adenocarcinomas will, therefore, contain a high proportion of resected specimens.

The course of the disease in patients with adenocarcinomas is not easy to discover. As in other inquiries, the small numbers make valid comparisons with other types difficult. In the report by Buchberg, Lubliner and Rubin

undifferentiated group. In the series of Harnett (1952) on the other hand, there were only 21 known adenocarcinomas among 236 patients, with a mean duration of 3·9 months, compared with 11·4 for squamous and 7·3 for undifferentiated tumours. Another report gives a 2-year survival rate of 7 per cent among 43 patients and 23 per cent and 9 per cent for the other two histological groups (United Birmingham Hospitals 1954). In the present investigation there were only 15 patients known to have an adenocarcinoma who were not treated surgically or by radiotherapy; all died within a year of diagnosis. The 1-year survival rates for squamous and undifferentiated groups were 25 per cent and 12 per cent respectively. A similar pattern is seen in necropsy series, where selection is less likely to affect the comparison. Bryson and Spencer (1951) found the total duration from the first recorded symptom to be 25 weeks for the small group of adenocarcinomas, 32 weeks for squamous and 21 weeks for 'oat-cell' tumours.

Although the disease among untreated patients with adenocarcinomas appears to be rapidly fatal after diagnosis, the survival rate of those who have had the tumour removed has been reported to be about the same as that of patients with a squamous tumour (Bignall and Moon 1955, Kirklin, McDonald, Clagett, Moersch and Gage 1955; Belcher 1956; Kjaer 1957). In other reports, however, the rate has been much lower and more close to that of the undifferentiated group (United Birmingham Hospitals 1954; Gifford and

Waddington 1957). One hypothesis to explain the short survival of untreat[ed] patients and long survival of those who have had the primary removed coul[d] be that the adenocarcinomas have relatively little tendency to spread locally but tend to spread by the blood stream frequently and early. The selected group having a resection might then contain a high proportion of patients who have safely passed through the period of greatest danger in the evolution of the disease. The results of treatment, are, however, influenced by so many other separate or correlated factors that it is difficult to separate the effect of histological type only, particularly in such a small group as the adenocarcinomas.

In summary, the adenocarcinomas appear to present a different pattern from the squamous and undifferentiated tumours. They may be unrelated to smoking (see p. 63) and relatively less uncommon in women and, possibly, young people. They are predominantly peripherally situated. More in consequence are detected by routine radiography in patients without symptoms and more are associated with long histories of illness. They tend to spread more readily by the bloodstream, and, if not removed, are more rapidly fatal once symptoms have appeared, than squamous tumours. If the tumour can be removed, however, the prognosis is probably better.

Bronchiolar ('Alveolar Cell') Carcinoma

The first record of this type of tumour is said to be that of Malassez (1876). Reviews of the reported cases have been published by Neubuerger and Geever (1942), Swan (1949), and Storey, Knudtson and Lawrence (1953), who analysed 205 collected cases, including 37 of their own. The tumours have been given many names—Liebow (1952) lists 36 of them—including 'alveolar cell tumour' and 'pulmonary adenomatosis'. It seems likely that the tumours called 'pulmonary adenomatosis'—a name implying a benign condition—do not differ in gross or microscopic appearances and behaviour from those called by othe[r] names; and the origin of the tumours in 'alveolar cells' is not proved (see p. 121). 'Bronchiolar carcinoma' appears therefore to be more acceptable.

Storey, Knudtson and Lawrence (1953) give the following criteria for diagnosis: a tumour characterised by alveoli lined by epithelial or cuboidal cells with eosinophilic cytoplasm and basally placed nuclei: preservation of the pulmonary architecture; absence of an intrinsic tumour of the bronchus; absence of evidence of primary adenocarcinoma in any other part of the body. The tumours appear to be closer histologically to the adenocarcinomas than to other types.

Among the 205 collected cases there was evidence of metastases in 54 per cent, with approximately equal proportions with metastases in regional nodes only, regional plus distant, and distant sites only. The most frequent sites of involvement outside the thorax were the liver, bones, adrenal, brain and kidney. In about half the patients there were lesions in both lungs. It has been postulated that there are several sites of origin within the lung (Delarue and Graham 1949); but there appears to be more evidence that the tumour arises at one place only (Herbert 1944, 1946) and that the multiple lung lesions are the result of bronchial embolism by tumour fragments (Hutchinson

1952), lymphatic spread (Weller 1929), or spread by the blood stream (Tillett and Hirsch 1952). The incidence of bronchiolar carcinoma has been reported to be as high as 5 per cent of all lung cancers (Storey, Knudtson and Lawrence 1953); but the estimate will depend among other factors on the criteria used and there may be no recognizable dividing line between the bronchiolar tumour and the peripheral adenocarcinomas In the Brompton and Royal Marsden Hospitals series there were only 4 out of the 1,024 with known histological type. In the reported examples there have been almost as many women as men—a further similarity with the adenocarcinomas.

There are no characteristic symptom patterns. The production of large amounts of clear frothy sputum has been reported to be a prominent feature, but this appears from the collected series to be quite exceptional 17 per cent had no sputum at all and 56 per cent coughed up less than 90 ml. daily; but the sputum was more commonly mucoid than purulent. On the other hand a few patients have produced extremely large quantities of sputum, and Levinsky and Kern (1952) reported a patient who spat up about 78 litres in less than 4 months with consequent serious fluid, electrolyte and protein depletion. Warfvinger (1955) found in one patient considerable increase of a protein fraction of the sputum normally absent or present only in small amounts.

The disease appears to evolve slowly; Storey, Knudtson and Lawrence (1953) found that in 41 per cent of the recorded cases the illness lasted more than a year and in 23 per cent more than 2 years. It tends to cause a long debilitating illness ending with gross respiratory insufficiency and asphyxia. Because of the peripheral origin and slow evolution of the tumour there is considerable variation in the stage of the disease at which the diagnosis is made. The commonest radiographic appearances in 153 of the reported cases were: a solitary peripheral nodule (26 per cent), bilateral nodules in all zones (20 per cent) or consolidation of all or part of a lobe (16 per cent), in other cases there were [illegible]
in one ar[illegible]
(5 per cer[illegible]
[illegible]

who had some form of lung resection—24 lobectomies, 18 pneumonectomies, 4 segmental resections and 3 local enucleations. In a few patients a second resection had been done for a recurrence. 5 patients were known to be alive and well more than 5 years after resection (Watson and Smith 1951; Škorpil 1942–43; Osserman and Neuhof 1950; Delarue and Graham 1949). Mears, Kirklin and Woolner (1954) reported 13 resections from the Mayo Clinic, 10 lobectomies and 3 pneumonectomies 2 patients died soon after operation and 2 from other causes. The tumour was known to have recurred in 7 and 5 had died. Only 2 patients were still alive without recurrence, 1 and 4 years after operation. Radiotherapy has been reported useless (Weir 1950; King and Carroll 1950; Abbott 1951, Mears, Kirklin and Woolner 1954)

It has been suggested that chronic inflammation may be a factor in the

development of these tumours. Beaver and Shapiro (1956) described 7 cases in which bronchiolar carcinomas were found associated with areas of chronic lung inflammation. In another case there was alveolar hyperplasia and an area showing the 'typical pattern of alveolar carcinoma' associated with chronic bronchiectasis. They pointed out that nearly two-thirds of the patients in the published reports had a history of previous lung disease and over 80 per cent of those in whom sufficient details were available had gross or microscopic evidence of chronic inflammation. Spain (1957) found various degrees of interstitial inflammation and fibrosis of the lung near to or remote from the tumour in 12 of 16 cases of bronchiolar cancer; and Zatuchni, Campb and Zarafonetis (1953) described three cases in patients with scleroderm It may be true that the alveolar hyperplasia found in chronic inflammation is stage in the evolution of bronchiolar carcinoma and that the association o the tumour with previous chronic lung infection is not fortuitous, but the varying criteria of histological diagnosis of bronchiolar carcinoma may cause confusion. Good, McDonald, Clagett and Griffith (1950), for instance, stated that 'in typical alveolar cell tumours the septa are not thickened'; and they believed it essential for diagnosis to have neither thickened alveolar septa nor more than slight evidence of inflammatory reaction.

There appears to be no good evidence that bronchiolar cancers differ essentially from adenocarcinomas. They are tumours that arise peripherally and appear to extend as a film on the walls of the alveoli: they spread to the lymph nodes less readily than other types and to the same or other lung more readily. The long duration of the illness reflects the relatively small tendency to spread by the blood vessels and the sluggish progress of the lung lesions, and the comparative failure of resection and radiotherapy and the manner of dying result from the widespread involvement of the lungs themselves.

CHAPTER XVII

THE EFFECT OF AGE AND SEX

J. R. Bignall

Carcinoma of the Lung in the Young and Old

THE effect of age and sex on the mortality rate for lung cancer has been discussed in Chapter II. This rate will, to a large extent, reflect the morbidity rate or the prevalence rate, but the number of cases reported (the observed prevalence) in any series is likely to vary with time, the population at risk and the origin of the report. Lung cancer is very rare in persons under 30 years old. In our series between 1951 and 1955 there were only 2 out of 1,749 patients and both had undifferentiated tumours. Neuman, Ellis and McDonald (1956) found 5 patients in the records of the Mayo Clinic in the U.S A between 1945 and 1954. Fischer (1931) recorded 22 (1 per cent) under 20 years old from a total of 1,888, and Ochsner and De Bakey (1941) 36 (0 8 per cent) of 4,307. Anderson, Buechner, Yager and Ziskind (1954) refer to 16 case reports of histologically confirmed primary lung cancer in children under 15 years of age. 8 were boys and 8 girls, and there were no tumours of squamous cell type among them. In infants it is very rare indeed Hauser (1942) found only one case among 14,000 necropsies at Cleveland City Hospital, U S A., during 28 years. This was a 17 month old child who died from a highly undifferentiated lung tumour. There are two earlier reports: Schwyter (1928) of a 16 month girl with a widely metastasizing adenocarcinoma, and Beardsley (1933) of an adenocarcinoma in a girl of 10 months.

In the present series there were 44 under 40 years of age—36 men and 8 women. In 15 the histological type was unknown; the tumour was of the squamous variety in 9, undifferentiated in 16 and adenocarcinoma in 4 All had symptoms when the tumour was first discovered; and the illness began with a febrile episode in a high proportion (31 per cent) (Table XLVI). However, the duration of symptoms before diagnosis differed little from that of the older patients. Of the 14 patients who received neither surgical treatment nor radiotherapy only 1—a man with a squamous tumour—survived a year from diagnosis. The 1-year survival rate of patients of all ages was 17 per cent.

Neuman, Ellis and McDonald (1956) studied the course of the illness in 51 patients under 40 years old. Only 4 of the tumours were classed as squamous and there were 19 adenocarcinomas. In a group of 30 men under 40 years old reported by Anderson *et al* (1954) there were 11 with adenocarcinomas and 5 squamous. It is impossible to know whether the differences in histological types between these two series and our own are entirely due to differences in pathological interpretation. Anderson and his colleagues found a low incidence of cough and haemoptysis and frequent attacks of chest pain; they attributed

this to the large proportion of peripheral tumours (77 per cent) among their patients. Neuman, Ellis and McDonald, on the other hand, had only 29 per cent of peripheral growths among their young patients and found no important differences in the frequency of the various symptoms compared with published series of patients of all ages. Anderson *et al* thought that metastases were

TABLE XLVI

The Age of the Patients related to the Nature of the First Recorded Symptom, the Duration of Symptoms, Evidence of Metastases at First Examination, Treatment and Survival

	Proportion (per cent) within age groups			
	Under 40	40–49	50–69	70 or more
First symptom				
Fever	(31)	19	18	5
Haemoptysis	(10)	13	12	17
Duration of symptoms (months)				
Under 3	(41)	55	44	40
3–11	(48)	36	47	49
12 or more	(11)	9	9	11
Metastases at first examination	(39)	37	32	31
Treatment				
Thoracotomy	(41)	36	34	8
Resection	(23)	30	26	8
Radiotherapy	(46)	40	35	26
Survival for 1 year after diagnosis (untreated)	(7)	(7)	18	21

Percentages in brackets are based on less than 100 cases.

more frequently found at first examination in young people, but in our own experience and the report of Neuman, Ellis and McDonald, they were not more common than in the older patients, nor did the resection rate appear to be much different. 9 of the patients reported by Neuman *et al* had the tumour removed; 7 died within 5 to 13 months after operation and 2 lived more than 3 years. Anderson *et al* reported that 5 (25 per cent) of 20 untreated patients survived a year from the start of symptoms, with a median survival of 7·5 months. In an earlier study of the patients at the Royal Marsden Hospital and the Brompton Hospital the median survival time of 32 patients under 50 years old was also 7·5 months with 31 per cent living longer than a year; the duration of survival rose in each group studied, 46 per cent of those aged 70 or over living longer than a year, the differences, though small, appearing in patients with both differentiated and undifferentiated tumours (Bignall 1955*b*)

The prognosis after resection has been reported to be lower in both young and old patients. Gifford and Waddington (1957) found a 2-year survival rate

of 38 per cent in those under 45, rising to 53 per cent in patients aged 55 to 59 and falling to 33 per cent in those over 60. But in another series (Bignall and Moon 1955) there appeared to be no regular pattern and the rate for those under 45 (53 per cent for 2 years) was almost the same as for those between 50 and 54 (51 per cent) and 60 to 64 years old (55 per cent). On the other hand, in one series the survival rate after surgical treatment or radical radiotherapy fell from 21 per cent in those under 45 to 10 per cent in those aged 60 to 69 (Registrar General 1957).

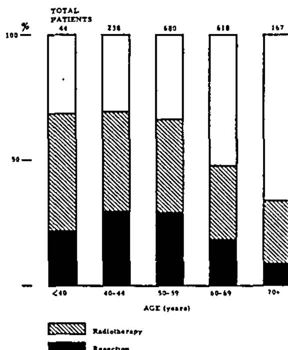


FIG 44

The treatment given to patients of different ages.

The oldest reported patient with lung cancer was a woman of 101 (Howell 1957). She had widely disseminated nodules of adenocarcinoma in both lower lobes with a single metastasis in the suprarenal. Relatively few patients with lung cancer in the eighth and ninth decades are seen at the Brompton and Royal Marsden Hospitals; there were only 6 over 80 years old in the present series. Febrile illnesses were a less common start of the illness in those over 70. Aufses (1953), in a study of 201 patients aged 65 or more, also found a low incidence of pneumonia as the first recorded sign—it occurred in only 5 cases. The older patients in our series had slightly longer illnesses and evidence of metastases when first examined was a little less frequent. Far fewer had the tumour resected—only 8 per cent of those 70 years old or more (Fig 44).

The higher survival rate among the patients not treated by surgery or radiotherapy (Fig. 45) may reflect the general tendency for the disease to run a slower course—to be less malignant; but it may also be affected by the smaller proportion drawn off from the 'untreated' group into the surgical and radiotherapy groups. This might have the effect of weighting the 'untreated' series in favour of long survival.

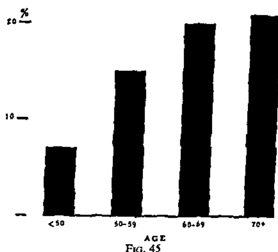


FIG. 45

The proportion of patients of different ages not treated by surgery or radiotherapy who lived for a year after first attending hospital

LUNG CANCER IN WOMEN

Adenocarcinomas form a higher proportion of all lung cancers in women than in men in this country. In the present series the ratio of men to women was almost 4 to 1 among those with adenocarcinomas but 11 to 1 among those with squamous cancers (Table XLVII): and there was a relatively high proportion of women among the adenocarcinomas in all age groups. Similar differences occurred in the clinical series of Doll and Hill (1952) (Doll, personal communication), and the necropsy study of Galluzzi and Payne (personal communication). In the other important factor—the site of the tumour—there were also differences between the sexes (see p. 166).

Pain and haemoptysis were slightly less frequently recorded as the first symptom in women than in men (Table XLVIII). In the case of pain the difference is probably not due to random sampling variations as it appears at all ages, except among the few aged 70 and over. It is unlikely that the age and sex of the patients influenced the clinician when he recorded the first symptom of the illness from the patient's story. It is possible that women might less frequently describe pain as the start of their illness even though they had experienced it or more frequently describe the less obtrusive symptoms; but it seems unlikely. It is reasonable, therefore, to conclude that

the illness may, in fact, begin less commonly with pain in the chest in women, who more frequently complain of such relatively unobtrusive symptoms as malaise, loss of weight and dyspnoea. The relative infrequency of chest pain may be related to the smaller incidence of upper lobe tumours.

Although the illness tended to have a more insidious beginning, the duration before examination at hospital was much the same When they were examined, however, a higher proportion were found to have regional or distant

TABLE XLVII

The Ratio of Men to Women with Tumours of the Three Main Histological Types at Different Ages in the Present Series (BH/RMH), a Necropsy Series (Galluzzi and Payne (personal communication)) and the Clinical Series of Doll and Hill (1952) (Doll, personal communication)

Series	*Total patients*	*Male/Female ratio at age (years)*				
		Under 40	40–49	50–59	*60 or more*	*All ages*
BH/RMH 1951–55						
Squamous	446	∞ : 1	34·0 : 1	10·6 : 1	9·4 : 1	11·4 : 1
Undifferentiated	470	1·7 : 1	7·2 : 1	11·6 : 1	6·4 : 1	7·6 : 1
Adenocarcinoma	69	3·0 : 1	3·0 : 1	4·5 : 1	3·8 : 1	3·9 : 1
NECROPSY SERIES (*Galluzzi and Payne*) 1948–52						
Squamous	177	3·0 : 1	5·5 : 1	13·7 : 1	8·3 : 1	8·3 : 1
Undifferentiated	470	1·4 : 1	5·8 : 1	5·4 : 1	3·9 : 1	4·3 : 1
Adenocarcinoma	93	0·3 : 1	3·0 : 1	6·0 : 1	3·0 : 1	3·2 : 1
		Under 45	45–54	55–64	65–74	*All ages*
CLINICAL SERIES (*Doll and Hill*) 1948–52						
Squamous	493	∞ : 1	31·0 : 1	32·7 : 1	8·8 : 1	26·4 : 1
Undifferentiated	341	4·0 : 1	6·9 : 1	12·5 : 1	14·0 : 1	8·0 : 1
Adenocarcinoma	43	3·5 : 1	4·3 : 1	2·6 : 1	2·6 : 1	3·3 : 1

metastases; consequently a lower proportion had a thoracotomy (Fig 46) But in only 3 of the 37 women operated on was the cancer judged to be inoperable and in about a third the lesion was limited enough for a lobectomy to be performed—both findings reflecting the relatively high proportion of adenocarcinomas and peripheral lesions.

If the tumour is not removed, the total duration of the illness in women appears to be the same as in men (Bignall 1955*b*) In our series the proportions living for one and two years after diagnosis were similar in men and women

On the other hand, the chance of survival after resection has been report to be higher Among 453 surgically treated patients reported by Bignall an Moon (1955) there were 41 women and, although more of the women ha undifferentiated tumours, the 2- and 5-year survival rates among them were 65 per cent and 57 per cent compared with 56 per cent and 31 per cent for men. Gifford and Waddington (1957), however, found 2- and 5-year rates of only 38 per cent and 25 per cent among the 39 women who survived operation,

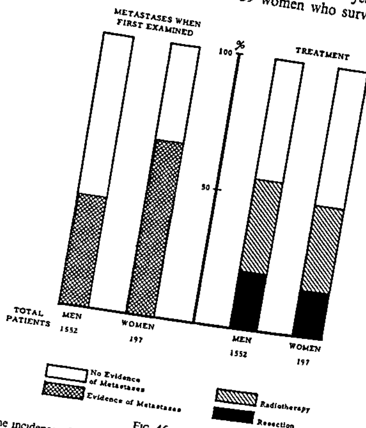


FIG 46
The incidence of metastases when first examined at hospital and the treatment given to men and women.

compared with 45 per cent and 29 per cent of men. Moreover, in the Brompton Hospital series (p. 228) there were no important differences in survival up to 5 years from operation.

Galluzzi and Payne (1955) observed no differences in the tendency of men and women to develop metastases. When allowance was made for the differing proportions of the histological types at each age, the incidence of metastases was broadly similar at all ages except in the few patients under 45. In these younger individuals there was a considerable excess of metastases in men, caused almost entirely by a much greater incidence of secondaries in the

TABLE XLVIII

The Nature of the First Symptom, Evidence of Metastases at First Examination, Treatment and Survival Untreated in Men (1,552) and in Women (197).

	Men	*Women*
FIRST SYMPTOM		
Pain	19%	13%
Haemoptysis	13%	10%
Metastases	2%	4%
METASTASES AT FIRST EXAMINATION	31%	46%
Distant Metastases	11%	19%
TREATMENT		
Thoracotomy	31%	19%
Resection	23%	17%
Pneumonectomy	17%	12%
Lobectomy	6%	5%
Survived 1 year from diagnosis (untreated)	18%	14%

adrenals. A detailed study of the incidence of brain metastases (Galluzzi and Payne 1956) also showed no important sex differences at any age.

Too little is known about the course of lung cancer in women to justify firm conclusions. There appear, however, to be no major differences that cannot be explained by the known histological and topographical pattern of the tumours; and there is, at present, little evidence of a different reaction of the body to the presence of the tumour.

CHAPTER XVIII

THE EFFECT OF THE SITUATION OF THE TUMOUR AND THE LENGTH OF THE ILLNESS BEFORE DIAGNOSIS

J. R. Bignall

The Effect of the Situation of the Tumour

The situation of the tumour has considerable influence on the course of the disease. It helps to determine the nature of the symptom pattern and materially affects the progress of the illness.

It is not surprising that tumours of the main and lower lobe bronchi frequently show their presence with a febrile illness; for these bronchi are less able to withstand progressive narrowing and interference with the ciliary mechanism without infection of the lung (Table XLIX) In this series the

Table XLIX

The First Recorded Symptom Related to the Site of the Tumour

Site	Total known	First symptom (per cent of total known)						
		Pain	Haem	Fever	Cough	Meta-stases	Other	Nil
Upper lobes	709	21	12	15	24	1	23	4
Lower lobes	388	16	16	25	22	1	14	6
Main bronchus	257	14	14	24	25	2	20	1
Right middle lobe	38	(16)	(13)	(11)	(31)	(11)	(16)	(2)
Lobar site not known	325	19	9	11	27	7	24	3
Total	1,717	18	13	18	24	2	21	4

Percentages in brackets are based on less than 100 cases

upper lobe tumours tended to be associated with an illness beginning with the less obtrusive symptoms such as loss of weight, malaise and dyspnoea or with chest pain unaccompanied by fever. Some patients with upper lobe lesions had tumours at the apex that showed themselves by shoulder and arm [illegible]

adenocarcinomas in the upper lobes. These, being largely [illegible] might more easily produce pain from pleural and chest wall invasion. The

shape and size of the upper lobe may also be a factor in making pain from peripheral extension of all types of tumour a more frequent complaint.

The site appears to have little effect on the length of history before diagnosis. Peripherally placed lesions might be expected to evolve with fewer acute and distressing symptoms such as haemoptysis and feverish illnesses—symptoms that might make the patient seek advice without delay. Adenocarcinomas, many of which are peripheral, do indeed tend to cause longer illnesses before diagnosis; but in this series patients with main bronchus lesions did not in general have shorter histories than those with tumours in the lobes of the lung, although many of these were remote from the large lobar bronchi. Peripheral tumours are likely to be older than central ones when they are discovered; but there is no evidence that they cause longer illnesses once symptoms have appeared.

Although the situation of the tumour may have little effect on the length of history before diagnosis, it certainly influences the future course of the disease. Because of the peculiarities of the lymph drainage of the lungs, metastases from right upper lobe tumours may reach the paratracheal nodes and cause venous obstruction, or the neck nodes and be clinically obvious, before those of the left upper lobe or both lower lobes. Of the patients with right upper lobe lesions, there were 19 per cent with manifest node metastases without distant metastases when first examined, but only 16 per cent of left upper lobe and 11 per cent of all lower lobe tumours Main bronchus lesions, however, gave the highest incidence (22 per cent); and in both lower lobe and main bronchus lesions the incidence was higher with left-sided tumours, probably because involvement of the left recurrent laryngeal nerve gives such obvious abnormal symptoms and signs Thus, fewer patients with upper lobe and main bronchus tumours are accepted for thoracotomy and have the cancer removed (Table L; Fig. 47) Indeed, only a small proportion of the main bronchus lesions are resected, for, in addition to the higher incidence of metastases, there is in many cases the technical impossibility of complete excision

Main bronchus tumours appear to cause symptoms at a later stage of their development, so that more of them have spread to the nodes by the time they are discovered. As they arise in large bronchi they are less likely to cause symptoms from bronchial narrowing or radiographic shadows of lung collapse or consolidation. Moreover, the tumour itself may not be detectable on the x-ray. Only 1 per cent of those known to have main bronchus tumours had no symptoms when the abnormality was found The late stage of many main bronchus lesions is reflected in the short survival of the untreated patients after diagnosis In this series only 11 per cent lived a year or longer, compared with 22 per cent of those with upper lobe and 25 per cent with lower lobe tumours.

The survival rate without resection or radiotherapy was slightly higher in patients with lesions of the left lung, though this may well have been a chance finding. The risk of dying soon after operation also appears to be smaller with operations on this side. Bignall and Moon (1955) reported a 12 per cent

mortality within 2 months with cancers on the right and 8 per cent on the left Gifford and Waddington (1957) found larger differences: 33 per cent compared with 17 per cent in 312 pneumonectomies and 16 per cent and 12 per cent in 136 lobectomies. The difference seemed to be mainly caused by greater risk of 'cardiopulmonary failure' after right-sided resection. In a series of 599 resections at the Brompton Hospital between 1940 and 1955 there were 78

TABLE L

The Site of the Tumour Related to Evidence of Metastases at Diagnosis, Thoracotomy, Resection and Survival

		Total cases	Proportion (per cent)			Untreated per cent living 1 year after diagnosis
			Metastases at first examination	Thoracotomy	Resection	
UPPER LOBE	R	377	30	33	25	20
	L	343	21	42	32	25
	Both	720	26	37	28	22
LOWER LOBE	R	215	18	46	41	(20)
	L	179	23	42	34	(30)
	Both	394	20	44	38	25
MAIN BRONCHUS	R	137	23	17	13	(12)
	L	126	36	14	7	(10)
	Both	263	29	15	10	11
RIGHT MIDDLE LOBE		38	(34)	(42)	(26)	(15)
TOTAL RIGHT LUNG		932	33	29	23	16
TOTAL LEFT LUNG		797	32	31	23	19
NOT KNOWN		20	—	—	—	—
TOTAL		1,749	33	29	23	17

Percentages in brackets are based on less than 100 cases

deaths within 2 months of operation, 16 per cent of 311 on the right and [illegible] the left.

[illegible] the prognosis seems to be [illegible] ald and Harrington 1951; [illegible] 1957). A possible explana- [illegible] be found in the anatomy of [illegible] lymphatics from the lower third of the left lung, as well as some of those from the middle third, drain through the bifurcation nodes into the right para-tracheal chain. Warren and

Drinker (1942) demonstrated in dogs that the greater part of the lymph from both lungs eventually passed into the vessels in the right para-tracheal region; only a small amount from the left lung entered the blood stream from the left paratracheal system. The distribution of metastases could not be expected to follow strictly the physiological path of the lymph, for once a pathway becomes blocked by a tumour the lymph stream is probably diverted into other channels. McCort and Robbins (1951) investigated the site of the metastases in 115 patients who had a thoracotomy for bronchial carcinoma Although 11 of 22 with right upper lobe tumours had right para-tracheal metastases, only 2 of 32 with left upper lobe tumours had metastases in the left para-tracheal nodes

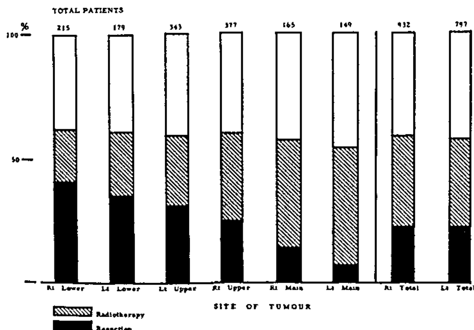


FIG 47

The treatment given to patients with cancers of different sites in the lung.

and three had involvement of nodes on the right side. There was, however, no similar suggestion of crossed dissemination from left lower tumours Nohl (1956) from a study of 100 lung tumours removed at operation concluded that tumours of the lower lobes on both sides have a greater tendency to metastasize locally than those of the upper lobes (see p. 136) But investigation of the spread of lung cancer in the mediastinum clearly requires post-mortem examination, and evidence derived only from clinical, radiographic and operative findings is incomplete However, the poor survival after removal of left-sided cancers, particularly of the left lower lobe, may well be largely the result of some patients having tumour tissue in the right upper mediastinal nodes, which are, of course, inaccessible at operation (Bignall and Moon 1955)

THE EFFECT OF THE DURATION OF THE SYMPTOMS

The beginning of the illness is not the start of the disease. The tumours show themselves at varying stages of their evolution depending on their site and the rate of growth and spread. The duration of symptoms before diagnosis is not, therefore, an accurate measure of the age of the tumour. Some patients with short illnesses have produced symptoms early while others have 'old' tumours that have produced them late. As the duration of symptoms in groups of patients lengthens, so the proportion of 'young' tumours within the group decreases. Some tumours spread outside the lung early, others late and some not at all; and the proportions of cancers growing slowly and having little tendency to spread by the lymphatics or the blood stream increases with the lengthening duration of illness. It could be expected, therefore, that the chances of successfully treating a patient with lung cancer will be higher in those with short or very long histories—the former group containing more with early tumours and the latter more with indolent cancers.

Among the patients in this series the proportion without clinical or radiographic evidence of metastases when first examined was 80 per cent in those with symptoms for less than a month; it fell to 63 per cent of those with symptoms for 6 to 11 months, but rose again to 79 per cent among those whose illness was recorded as having lasted a year or longer (Table LI). The proportion with regional node metastases rose from 10 per cent in the group with the shortest history to 24 per cent in those with symptoms for 6 to 11 months but fell to 13 per cent in those with the longest illnesses. The changes

TABLE LI

The Duration of Symptoms Before Examination Related to the Evidence of Metastases at First Examination, Treatment and Survival Untreated

	Proportion (per cent) within the group					
	No symptoms	*Duration of symptoms (months)*				
		0	1–2	3–5	6–11	12 *or more*
METASTASES AT FIRST EXAMINATION						
Regional only	14	10	26	23	24	13
Distant with or without regional	1	10	12	11	13	8
None	85	80	62	66	63	79
TREATMENT						
Resection	61	25	21	20	21	28
Radiotherapy	12	30	35	38	33	29
Survived 1 year from diagnosis (untreated)	(11)	(25)	17	12	21	(17)

Percentages in brackets are based on less than 100 cases

in the proportions of distant metastases are smaller, but of the same pattern. Similar findings have been reported by McKenzie (1956) from a study of more than 10,000 case records. He found that the median duration of symptoms decreased with the increasing extent of the lesions at diagnosis; it was 5·9 months for those classed as having tumours confined to the lung and 4·9 months for those with distant metastases; only 6 per cent of the former group had histories of less than 2 months, compared with 14 per cent of the latter

The proportion of patients who have a resection varies with the length of history, as would be expected from these variations in the stage of the disease (Fig 48)

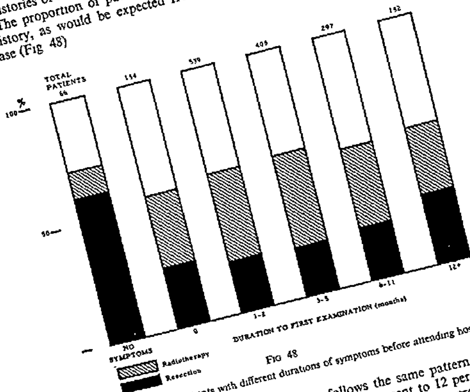


Fig 48

The treatment given to patients with different durations of symptoms before attending hospital

The survival rate of untreated patients follows the same pattern· thus, in the present series the one-year rate fell from 25 per cent to 12 per cent as the duration of symptom lengthened but rose to 17 per cent in the group with the longest histories Similar variations of the survival rates with the length of history before diagnosis have been reported for cancers at other sites (the reports were reviewed by Harnett (1953)), and for the lung (McKenzie 1956; Registrar General 1957)

Among patients who have had the primary removed the prognosis also varies with the duration of symptoms before operation Bignall and Moon (1955) found that the 2-year survival rate among 453 patients treated surgically

varied from 53 per cent in those with symptoms for less than 3 months to 39 per cent with 6 to 8 months history and 54 per cent with a year or longer; and Gifford and Waddington (1957), in a study of 448 patients, reported 2-year rates of 46 per cent with less than 6 months history, 36 per cent with 6 to 9 months and 59 per cent with symptoms for more than 9 months.

LUNG CANCER DETECTED WITHOUT SYMPTOMS

In this series 66 patients were recorded to have had no symptoms when the radiographic abnormality in the lung field was detected. Only 3 were known to have main bronchus tumours. When they were examined at the hospitals 10 (14 per cent) of them had evidence of metastases The proportions of the three histological types were approximately the same as among the patients with symptoms Thoracotomy was done in a high proportion—64 per cent—and in only 2 patients was the growth too extensive to be resected Of the 40 patients who had a resection 29 (73 per cent) were alive a year later and 18 (62 per cent) two years. 8 were treated by radiotherapy and none survived a year There were 18 not treated by these methods; 2 have, unfortunately, been lost sight of. The 1-year survival rate, counting these 2 patients as dead, is only 11 per cent; but if they are both alive it would be 22 per cent—similar to the rate for those with symptoms of less than a month's duration when diagnosed.

Lung cancer detected by mass radiography surveys is not necessarily 'silent'. Boucot and Sokoloff (1954) reported 77 cases among 142,156 persons x-rayed; but only 7 were truly without symptoms. 43 considered themselves to be well but some symptoms that could reasonably be attributed to the cancer were elicited on careful questioning in all of them; a further 27 had already consulted their doctors because of symptoms. Brocard, Choffel, Bouvier, Solignac and Ledu (1955) found 24 without symptoms among 44 picked up by radiographic survey. Only 9 of these were operated on; 5 refused operation and the condition was considered inoperable in 10 by the time the diagnosis was established—often after considerable delay. McBurney, Kirklin and Hood (1955) found 29 cases of 'asymptomatic' lung cancer among approximately 1,600 case records at the Mayo Clinic. They excluded 'smoker's cough' as a symptom of the cancer The interval from detection of the lesions to resection—which was carried out in all cases—ranged from 3 days to 4 years. There were 12 adenocarcinomas, 4 squamous and 13 'large cell' or 'small cell' tumours. All but two of the cancers were classed as peripheral. Of the 29 patients, 23 (79 per cent) survived the first year. The authors state that the survival figures were 'not dissimilar to those found after resection for bronchogenic carcinoma in general'. However, as the 'operability rate' was higher, the experience of the whole group was better.

Garland (1955) summarised the findings in a number of reports on the treatment of patients detected by survey. Many factors influence treatment and it is not surprising that the proportion resected varied from 22 per cent to 60 per cent in six reports. The combined results of three follow-up reports

after resection gave a 3-year survival rate of 29 per cent among 132 patients. Overholt, Bongas and Woods (1955) reported a 30 per cent three-year survival rate among 30 patients, 23 (77 per cent) of whom had a resection.

The experience of the patients in the present series also indicates that the chances of successfully treating lung cancer are greater in those patients who have had no symptoms at all or such unobtrusive ones that they were overlooked at the time the x-ray abnormality was found On the other hand, it is not surprising that some patients have irremovable tumours or die with metastases after resection

'Early' Lung Cancers

The so-called 'silent phase' of lung cancers is not necessarily the phase during which the growth is limited to the lung From the moment that a neoplasm begins to form there is the possibility of spread by the lymphatics or the blood The patient may die with metastases while the primary is still minute. Willis (1948) described such a condition in a man with two cystic adenocarcinomas up to 5 cm diameter in the brain and a primary tumour only 4 mm diameter in the left upper lobe of the lung. On the other hand, some cancers kill the patients without producing any macroscopic metastases at all; and primary tumours have been surgically removed with success after being observed radiographically for many years—in one case for as long as 9 years (Overholt and Schmidt 1949) It is misleading to describe lung tumours as 'early' or 'late' The age of a tumour cannot be determined unless the time of its birth is known, and, because of the great variation in speed of growth and spread, it cannot be inferred from the state of the tumour when first discovered. Except in experimental studies, the temporal stage of evolution of a cancer is indeterminate. The cancer itself can be described topographically; and the stage of the disease by reference to the disorder of function that it has produced In the symptomless patient the disorder of function may be slight or there may be none at all; yet the cancer may be anatomically extensive 'Early diagnosis' might be used to describe the detection of cancers causing little or no disorder of function, but 'diagnosis of early cancer' is meaningless in clinical medicine Mass or routine radiotherapy can lead to 'early diagnosis': it does not necessarily detect 'early' cancers

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varied from 53 per cent in those with symptoms for less than 3 months to 39 per cent with 6 to 8 months history and 54 per cent with a year or longer, and Gifford and Waddington (1957), in a study of 448 patients, reported 2-year rates of 46 per cent with less than 6 months history, 36 per cent with 6 to 9 months and 59 per cent with symptoms for more than 9 months.

Lung Cancer Detected Without Symptoms

In this series 66 patients were recorded to have had no symptoms when the radiographic abnormality in the lung field was detected. Only 3 were known to have main bronchus tumours. When they were examined at the hospitals 10 (14 per cent) of them had evidence of metastases. The proportion of the three histological types were approximately the same as among the patients with symptoms. Thoracotomy was done in a high proportion—64 per cent—and in only 2 patients was the growth too extensive to be resected. Of the 40 patients who had a resection 29 (73 per cent) were alive a year later and 18 (62 per cent) two years. 8 were treated by radiotherapy and none survived a year. There were 18 not treated by these methods; 2 have, unfortunately, been lost sight of. The 1-year survival rate, counting these 2 patients as dead, is only 11 per cent, but if they are both alive it would be 22 per cent—similar to the rate for those with symptoms of less than a month's duration when diagnosed.

Lung cancer detected by mass radiography surveys is not necessarily 'silent'. Boucot and Sokoloff (1954) reported 77 cases among 142,156 persons x-rayed; but only 7 were truly without symptoms. 43 considered themselves to be well but some symptoms that could reasonably be attributed to the cancer were elicited on careful questioning in all of them; a further 27 had already consulted their doctors because of symptoms. Brocard, Choffel, Bouvier, Solignac and Ledu (1955) found 24 without symptoms among 44 picked up by radiographic survey. Only 9 of these were operated on; 5 refused operation and the condition was considered inoperable in 10 by the time the diagnosis was established—often after considerable delay. McBurney, Kirklin and Hood (1955) found 29 cases of 'asymptomatic' lung cancer among approximately 1,600 case records at the Mayo Clinic. They excluded 'smoker's cough' as a symptom of the cancer. The interval from detection of the lesions to resection—which was carried out in all cases—ranged from 3 days to 4 years. There were 12 adenocarcinomas, 4 squamous and 13 'large cell' or 'small cell' tumours. All but two of the cancers were classed as peripheral. Of the 29 patients, 23 (79 per cent) survived the first year. The authors state that the survival figures were 'not dissimilar to those found after resection for bronchogenic carcinoma in general'. However, as the 'operability rate' was higher, the experience of the whole group was better.

Garland (1955) summarised the findings in a number of reports on the treatment of patients detected by survey. Many factors influence treatment and it is not surprising that the proportion resected varied from 22 per cent to 60 per cent in six reports. The combined results of three follow-up reports

after resection gave a 3-year survival rate of 29 per cent among 132 patients. Overholt, Bongas and Woods (1955) reported a 30 per cent three-year survival rate among 30 patients, 23 (77 per cent) of whom had a resection.

The experience of the patients in the present series also indicates that the chances of successfully treating lung cancer are greater in those patients who have had no symptoms at all or such unobtrusive ones that they were overlooked at the time the x-ray abnormality was found. On the other hand, it is not surprising that some patients have irremovable tumours or die with metastases after resection.

'Early' Lung Cancers

The so-called 'silent phase' of lung cancers is not necessarily the phase during which the growth is limited to the lung From the moment that a neoplasm begins to form there is the possibility of spread by the lymphatics or the blood The patient may die with metastases while the primary is still minute Willis (1948) described such a condition in a man with two cystic adenocarcinomas up to 5 cm diameter in the brain and a primary tumour only 4 mm. diameter in the left upper lobe of the lung. On the other hand, some cancers kill the patients without producing any macroscopic metastases at all; and primary tumours have been surgically removed with success after being observed radiographically for many years—in one case for as long as 9 years (Overholt and Schmidt 1949) It is misleading to describe lung tumours as 'early' or 'late'. The age of a tumour cannot be determined unless the time of its birth is known; and, because of the great variation in speed of growth and spread, it cannot be inferred from the state of the tumour when first discovered E
a cancer is in
and the stage
has produced In the symptomless patient the disorder of function may be slight or there may be none at all; yet the cancer may be anatomically extensive 'Early diagnosis' might be used to describe the detection of cancers causing little or no disorder of function, but 'diagnosis of early cancer' is meaningless in clinical medicine Mass or routine radiotherapy can lead to 'early diagnosis', it does not necessarily detect 'early' cancers

CHAPTER XIX

UNUSUAL MANIFESTATIONS

J. R. BIGNALL

NEUROPATHY AND MYOPATHY

NEUROLOGICAL syndromes have been recognised for many years in patients with cancer in whom there were no metastases affecting the nervous system. Posterior column degeneration secondary to changes in the posterior nerve roots were, for instance, described nearly 50 years ago (Williamson 1908). Weber and Hill reported the association of polyneuritis and carcinoma of the lung in a patient in 1933. More recently there have been several good accounts of the condition: subacute cerebellar degeneration in patients with cancers of the lung, breast, ovary and uterus (Brain, Daniel and Greenfield 1951); sensory neuropathy (Denny-Brown 1948), polyneuritis (Lennox and Prichard 1950), myopathy and neuropathy (Henson, Russell and Wilkinson 1954) in those with lung cancer. A case of sensory neuropathy associated with carcinoma of the oesophagus was reported by Dodgson and Hoffman (1953), and neuropathies or myopathies have also been described with carcinoma of the antrum (Hart 1950), and ovary (Henson, Russell and Wilkinson 1954). But with the exception of the report of Dodgson and Hoffman (1953), sensory neuropathies and polyneuritis have been recorded only in patients with carcinoma of the lung

Henson, Russell and Wilkinson (1954) found 15 (1·1 per cent) examples of the syndromes among 1,309 patients with lung cancer seen at the London Hospital between 1940 and 1952, and in 6 (2·2 per cent) of 276 necropsy records. Lennox and Prichard (1950) presented evidence that the association of polyneuritis with lung cancer was not fortuitous. From among the records of 50,000 admissions to the Hammersmith Hospital, London, they found 5 patients with the two conditions. There were 299 cases of lung cancer and 17 of polyneuritis of obscure origin, including the 5 with lung cancer. If no association had existed between the two, only 0·1 'cases' of the two together would have been expected in this material, and even allowing for probable inaccuracies of recording, the difference between the expected and observed associations seemed large enough to support the hypothesis that the conditions were not related only by chance

In the type with subacute cerebellar or spino-cerebellar degeneration the dominating manifestations are vertigo with cerebellar ataxia. There may be pyramidal signs and tremor of the extra-pyramidal type, euphoria or dementia. Muscular weakness and wasting, external ophthalmoplegia and bulbar palsy have been described and there may be sensory disturbances. Histological

examination may show degeneration of the cerebellar cortex, and a chronic, progressive degeneration and loss of motor neurones in the spinal cord and medulla (Henson, Russell and Wilkinson 1954). In the type with predominant sensory disturbances there may be cerebellar or extra-pyramidal signs or selective weakness and wasting of muscles. The degeneration and loss of neurones in the posterior root ganglia with degeneration of the posterior columns and peripheral nerves, show clinically as paraesthesiae, impairment of position sense, and pain and tenderness of the muscles. When there is a predominant neuromuscular disorder, the weakness and wasting may be generalised, or of a distribution consistent with a diagnosis of polyneuritis. There may be external ophthalmoplegia, bulbar palsy, ptosis, diplopia, weakness of the palate, dysarthria or dysphagia. The clinical picture may resemble that of myasthenia gravis.

Frequently the neurological manifestations are pleomorphic and remittent. The neuropathy may appear to become arrested. In the 19 patients reported by Henson, Russell and Wilkinson (1954) spontaneous arrest occurred in 2 and remission or apparent recovery in 5. Remission followed resection of the tumour in 2 instances, but the course is so variable in patients not treated surgically that the remissions cannot be claimed to have been caused by the resection. The clinical course of the cancer and the neuropathy are often clearly divorced. The symptoms of the neurological disorder may precede, coincide with, or follow the first manifestations of the lung cancer; and small or undetectable tumours may be accompanied by profound neuropathy.

It has been suggested that there is a causal relationship between the cancer and the disorder of the nervous system, possibly through disturbances of Vitamin B or pantothenic acid metabolism (Denny-Brown 1948), by means of ervous reflexes from the lung (Wyburn-Mason 1948), or by toxins from the ancer (Barraquer-Bordas and Lowenthal 1953). In a case reported by IcCaughey and Miller (1955) the presence of porphobilinogen in the urine s thought to be due to a secondary disturbance of porphyrin metabolism. nson, Russell and Wilkinson (1954), on the other hand, suggest that one dition does not cause the other, but that the two may be linked by a common sal factor. At present there appears to be insufficient evidence to support or te any of the hypotheses put forward.

PULMONARY OSTEOARTHROPATHY

t is well known that osteo-arthropathy occurs in patients with lung r. The reported frequency will, of course, vary with the origin of the report , in 1915, found only 9 instances of intrathoracic tumours among 144 ports of osteoarthropathy. Ray and Fisher (1953) found 14 examples cent) in 139 cases of histologically confirmed lung cancer; and Wierman, and McDonald (1954) found 25 (5 per cent) with joint manifestations 481 surgically treated patients.

joint symptoms may precede any other manifestations of the lung Harper and Patterson (1953) collected 47 published case reports of ence of events. In our own series there were 15 (1 per cent) of such

instances among 1,749 patients As in the case of the neuropathies there appears to be no relationship between the frequency with which the extrathoracic symptoms occur and the size of the tumour. There is, however, a suggestion that they are more common with peripheral tumours (Pattinson, Beck and Miller 1954; Ray and Fisher 1953).

The cause of the condition is unknown. Clinical observation suggests that infection of the lung plays no part. Ray and Fisher (1953) found no examples of osteoarthropathy among 57 patients with clinical or pathological evidence of infection of the lung, compared with 14 cases among 82 patients without evidence of infection—a finding that may be related to the greater frequency of joint involvement with peripheral growths. The link may be through the nervous system. The symptoms and signs almost invariably diminish dramatically as soon as the lung is removed, and frequently disappear entirely; but they also disappear without the lung being removed if the pulmonary artery is tied (Wyburn-Mason 1948) or the hilum dissected and the nerves cut (Hanson 1952) Furthermore, the same dramatic relief of symptoms and recession of signs can occur when the hilum is undisturbed but the vagus divided as far away from it as possible (Flavell 1956). The exact mechanism of the association is unknown It is probably a complex one. Patients with seemingly similar lung cancers behave in different ways and only a few of the many with peripheral tumours, for instance, have joint manifestations. After the symptoms have been relieved by resection of the lung, they may return if the growth recurs. Wierman, Clagett and McDonald (1954) report examples of this but they do not state where the tumour recurred and, in particular, its relation to the vagus nerves.

Endocrine Disturbances

Marie, who introduced the term 'osteo-arthropathie hypertrophiante pneumonique' in 1890, was mainly concerned with separating the condition from acromegaly, with which it was then confused. Patients with the clinical and radiographic picture of hypertrophic pulmonary arthropathy may indeed [illegible] described [illegible] lition to [illegible] ndocrine [illegible] ckening of the vault of the skull, enlargement of the sella turcica, and changes in secondary sexual characteristics. Although the anterior lobe of the pituitary showed hyperplasia of the eosinophil elements in some of the patients, no infiltration with metastatic tumour cells was found. In 2 of the patients there were also cortical adenomas of the adrenals. Fried suggests that the osteoarthropathy in these cases was caused by the endocrine dysfunction Two of Fried's patients had gynaecomastia. This has also been reported by Bloom (1948), but in his case there was a metastasis in the anterior lobe of the pituitary. On the other hand, in the case described by Fischl (1950) both the joint symptoms and the gynaecomastia improved after the primary tumour had been removed. Another of Fried's patients had insulin-resistant diabetes and

gynaecomastia, but there is no record of metastases being found in the pituitary. However, Arnstein (1933) reported 14 cases of diabetes insipidus in which there were metastases in the posterior pituitary from primaries in the lung or breast. Cushing's syndrome has been reported in association with lung cancer (Brown 1928; Thorn 1952; Montgomery, Ramsay, Robertson and Welbourn 1957), both with and without histological evidence of metastases in the pituitary or hyperplasia of the adrenal cortex. There may also be manifestations of Addison's disease (Fried 1933).

The Pancoast Syndrome

In 1924 Pancoast described three patients whose chest x-rays showed a homogenous density at the apex of the lung with erosion of the ribs and who also had pain in the shoulder and arm with wasting of the hand muscles, a drooping eyelid, and contracted pupil.

He reported 4 more cases in 1932, and, believing that the cause of the condition was a previously undescribed tumour arising from embryonic tissue derived from a branchial pouch, he named it the 'superior pulmonary sulcus tumour'. There had been a few isolated reports of the syndrome before Pancoast described it, the earliest being that of Hare (1838) (see p. 4). Herbert and Watson (1946) found 134 reported cases, to which they added 17 of their own. There have been a few instances of the condition being associated with what were thought to be primary tumours arising in the neck (Fried 1935; Graef and Steinberg 1936, Morris and Harken 1940; Herbert and Watson 1946); but in the majority there has been a bronchial carcinoma. The syndrome has also been described with primary tumours of the larynx, thyroid, and oesophagus, and with metastases from primaries of many other sites. In a few instances it has been attributed to conditions other than cancer: Hodgkin's disease (Herbert and Watson 1946); chronic non-tuberculous pneumonia (Ashe, McDonald and Clagett 1950); tuberculosis of the lung and pleura (Léri and Moulin de Teyssieu 1917; Pancoast 1932), tuberculous abscess (Mahoudeau and Courjaret 1945); neurinoma (Benedetti 1946); and lipoid infiltration in Hand-Schüller-Christian disease (Giova 1950).

Herbert and Watson (1946) list the manifestations in 151 recorded cases. In all but 11 there was an abnormal apical shadow in the chest x-ray; Horner's syndrome occurred in 133, shoulder pain in 129 and arm pain in 122; but paresis of muscles was recorded in only two-thirds of the patients. In the whole group, which included those with primary tumours outside the thorax, cough and dyspnoea were reported in less than a third and haemoptyses in only 6 instances. Thus, apart from the pain, there were no symptoms directing attention to the lungs in two-thirds of the patients.

Other Rare Manifestations

Recurrent Thrombophlebitis and Acanthosis Nigricans

Recurrent thrombophlebitis has for long been considered an early associate of visceral cancer. Fisher, Hochberg and Wilensky (1951) reported

4 patients in whom recurrent peripheral venous thrombosis preceded the discovery of the lung tumour by periods ranging from 1½ to 6 months. Similarly, acanthosis nigricans may be associated with visceral cancer. Curth (1943) found 384 reported cases including 3 of lung cancer, and Spear (1950) added another, the patient having an undifferentiated lung primary with no metastases in the suprarenals.

Crico-pharyngeus Palsy

Paralysis of the vocal cords from damage to the recurrent laryngeal nerves is common and well known. Such damage can also cause paresis of the crico-pharyngeus muscle with difficulty in swallowing fluids. Asherson (1952) reported two cases of bilateral laryngeal paralysis associated with dysphagia and coughing after swallowing fluids; pharyngograms showed a delay in the hypopharynx and pyriform fossae with the radio-opaque liquid overflowing into the glottis.

Abdominal Symptoms

Complaints of epigastric pain or discomfort, sometimes with flatulence, nausea, vomiting or anorexia, are not rare in association with a lung cancer. Wezel (1950) recorded 18 instances among 225 patients. In all of the 18 there were large mediastinal lymph nodes near the trachea or in the region of the bifurcation and it was suggested that the symptoms were caused by damage to the vagus nerve within the thorax. A further 15 patients were shown to have gastric or duodenal ulcers; and these also had mediastinal metastases

Heart Complications

Disordered heart rhythm can be produced by a lung cancer either directly by invasion of [illegible] or indirectly by damage to the vagus [illegible] nerve [illegible]. Scott and Garvin (1939) recorded 30 (26 per cent) instances of myocardial invasion in 115 cases of bronchial carcinoma at necropsy; and Pearson (1948) found some evidence of involvement of the heart in 17 (11 per cent) of 148, there being arhythmia in about two-thirds. Pearson (1950) reviewed 28 reported cases of arhythmia, 21 with auricular fibrillation or flutter, 4 with simple paroxysmal tachycardia, 1 with paroxysmal ventricular tachycardia, and 1 with constant tachycardia. He also reported a case of persistent bradycardia accompanied by attacks of ventricular asystole and unconsciousness. Two further examples of recurrent attacks of unconsciousness have been recorded by Davies (1957). The attacks were caused by sino-auricular block which may have been the result of vagal stimulation from the involvement of the left recurrent nerve in the tumour mass that was demonstrated by necropsy. Involvement of the pericardium by neoplastic tissue may cause a pericardial effusion or the clinical manifestations of constrictive pericarditis (Fischer 1948)

Regression of the Tumour

There are many reports of patients with histologically confirmed lung cancers receiving no specific treatment yet living for long periods. One

CHAPTER XX

THE COURSE OF LUNG CANCER

J. R. BIGNALL

THE course of lung cancer is governed by three factors: the malignant capabilities of the tumour; its situation in the lung; and the age of the patient. These factors are not independent. Lung cancer kills young patients quicker than old ones; and histologically identical tumours may have different degrees of malignancy because they arise from and evolve in young or old bodies. Moreover, tumours with similar powers of invasion and dissemination in similar hosts may kill differently because of their different positions in the lung. Indeed, the malignancy of a tumour cannot be defined at all without reference to its environment.

We do not know what determines the malignancy of a new growth except that the disease may be more malign in the young and less malign in the old. Cancers known to be caused by inhaled substances are predominantly of the squamous histological pattern; the cause of the adenocarcinomas is unknown; and the undifferentiated group may contain the less organized varieties of both these two types. As the squamous tumours appear to kill less quickly than the adenocarcinomas, malignancy may be said to be determined to a small extent by the cause of the cancer There is no evidence that it is influenced by the sex of the individual or by the sex hormones. The malignancy of lung cancers is, therefore, not determined by any factor that can at present be influenced by the patient himself, and it is the most powerful determinant of his fate. Nor—so far—can anyone else influence it

The site of a lung cancer may depend on the cause of it. Squamous cancers are predominantly in the main, lobar, and segmental bronchi, and adenocarcinomas more peripheral But the reasons why the malignant process begins in one particular small portion of the large area of the bronchial mucosa are unknown.

The three major factors in the course of the disease are, therefore, uncontrollable

The nature of the first symptom of ill-being is determined more by site than by malignancy. Tumours of the main or lower lobe bronchi tend to become manifest through feverish illnesses, and of the upper lobe bronchi through pain or the less obtrusive symptoms. Peripheral lesions may not cause local symptoms, but progress cryptically until regional or distant metastases become overt. There is no clear relationship between histological type and the way the illness begins, except that squamous tumours—possibly through their situation in the larger bronchi and their slow evolution—may be a little more likely to cause haemoptysis without preceding symptoms.

The evolution of the illness, on the other hand, is likely to be affected much more by the speed with which the cancer grows and spreads than by its situation. The stage of the cancer at which the symptoms appear may, indeed, be affected by the site For instance, a tumour must be larger, and therefore more advanced in its evolution, before it blocks a big bronchus But, once symptoms have appeared, the speed with which the pattern evolves is an expression of malignancy. The duration of the illness before the patient reaches hospital does not, however, express accurately the speed of development of the disease; it is too much influenced by such factors as the nature of the symptoms, the personality of the patient, and the actions of his medical advisers. Thus, haemoptysis and pain may cause more immediate concern than loss of weight and impairment of well-being, and both may bring the patient for advice more quickly, although haemoptysis as an initial symptom tends to be a manifestation of an 'earlier' cancer than does pain in the chest

The malignancy of the disease is expressed at this stage of its evolution by the presence of metastases. When first examined at hospital, the patients with the more malign tumours are more likely to have metastases, though the metastases may not be discoverable. Whether regional metastases are found at this stage depends to some extent on the situation of the tumour Lesions in the main and upper lobe bronchi, particularly on the right side, may—because of the anatomy of the lymphatics—be more easily detected than those of a lesion of similar maturity in the lower lobe. The dominant factor is, however, malignancy; and this may account both for the slightly greater incidence in women of metastases at the time of diagnosis—for in them squamous tumours are less common—and for the lower incidence of metastases with very short or very long histories

The fate of the patient may still be said to be decided by whether or not the malignant tissue can be surgically removed; and at this stage the age of the patient matters at least as much as the situation or malignant capabilities of the tumour. Although a few patients over 70 have had the cancer successfully resected, the chances of resection being feasible at this age are small. Only a relatively small proportion of old people with lung cancer are examined at hospital in this country at present, and few of those that are examined can be treated surgically. The disease progresses more slowly with advancing age and more might be operable on this account; but the operative risk also increases, and in many of them the cause of the cancer—cigarette smoking—is also the cause of its being inoperable, through the impairment of lung function by chronic bronchitis and emphysema At the other extreme, the young patients with good lung function and young cardiovascular systems tend to have more malignant cancers with a higher incidence of metastases at the first examination The situation of the tumour also affects the treatment, either by making removal impossible, as in some extensive main bronchus tumours, or by influencing the discovery of metastases, as in the case of right upper lobe lesions.

The duration of life, both in those treated surgically or by radiotherapy and in those who receive no potentially curative treatment, is almost always

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SECTION FIVE

THE TREATMENT OF CARCINOMA OF THE LUNG

. . . the writer may be permitted to express the hope that malignant disease of the lungs, so disastrous in its results, may perhaps in the near future be summarily dealt with in its incipiency, or at least modified in its progress, so as in some measure to assist in diminishing the sufferings of humanity.

Adler, I. (1912). *Primary Malignant Growths of the Lungs and Bronchi, p.* 109. *London Longmans, Green*

CHAPTER XXI

SURGICAL TREATMENT

W. P. CLELAND

THE aim of surgery in the treatment of lung cancer is the complete removal of the primary tumour and all regional lymphatics and lymph nodes. That this can be achieved is supported by well documented records of survival for 10 or more years after resection These are the favoured few; but they are enough to encourage the surgeon in his endeavours to add to their numbers

Regrettably, far too many patients are unfit for even an exploratory operation when first seen by the surgeon Probably less than 20 per cent of all patients seen at hospitals and special clinics are deemed to be operable. It is impossible to give a figure applicable to all units as the proportion varies with the individual surgical practice and the type of patient referred to the hospital (See p 169) Of those who are in the 'fortunate' group and who are submitted to an exploratory operation, approximately 60 per cent have an operation which can be regarded as having eradicated all the obvious tumour, about 20 per cent have palliative operations where removal cannot be regarded as complete and 20 per cent are found to be inoperable In the ensuing paragraphs it is proposed to consider the problems presented by these three groups of patients

Until recently surgery has been largely concerned with the perfection of the best possible operation for lung cancer, but of recent years more attention has been paid to the quality of survival after resection and to the welfare of those found unsuitable for radical treatment The present status of these procedures will be described

The clinical and statistical details have been largely obtained from my own personal records of 230 patients treated surgically during the last 12 years and supplemented where necessary from the records of patients treated by the surgical staff of the Brompton Hospital and surveyed by the Joint Consultation Clinic of the Royal Marsden and Brompton Hospitals

ASSESSMENT OF OPERABILITY

The assessment of operability is largely a personal affair and it is difficult to do more than lay down the general principles affecting the selection of cases for operation, pointing out that these are merely guides for assessment. The strictness of the criteria for operation will obviously affect the resectability rate, a conservative approach being associated with a high resection rate and vice versa Similarly the resection rate will be influenced by the approach of the surgeon to the problems involved—a bold policy should result in a higher resection rate Acceptance for operation must also be influenced by the

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ASSESSMENT OF OPERABILITY

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availability and efficiency of other alternative forms of treatment. For instance, where x-ray therapy is not readily available and surgical facilities are good, there is every justification for assessing patients leniently. The availability of radioactive gold grains has a similar effect for one knows that should the tumour be irremovable, the surgeon is in a position to do something to help the patient at the time of operation

In assessing operability, the following factors are taken into consideration·

The Primary Tumour

The most important consideration is the proximity of the tumour to the trachea as judged at bronchoscopy· this examination will demonstrate the upper limit of the tumour As there is only slow proximal extension microscopically, a clearance of 1 to 1·5 cm above the macroscopic level of the growth is probably sufficient to permit the complete removal of the tumour either by lobectomy or pneumonectomy. Although this clearance seems small, its validity is supported by the remarkably low incidence of recurrence in the stump after resection In only 4 of my personal series of 175 resections has a recurrence in the stump been demonstrated Resection can, however, still be carried out in border-line cases by including a portion of the main bronchus or of the trachea with the affected lobe or lung. This will be dealt with more fully under 'Sleeve Resection'.

Spread of Tumour

The tumour may directly invade the surrounding tissues or spread by the blood stream or lymphatics to more distant structures As a general rule, convincing evidence of such spread can be regarded as a contra-indication to resection It is easy to suspect but often difficult to be certain that such spread has occurred. It is also often difficult to distinguish between inflammatory and neoplastic changes, especially in the hilar and mediastinal lymph nodes and the pleura

Involvement of the Pleura

Pleural involvement may be the result of either inflammatory or neoplastic changes. The likelihood of one or the other occurring depends, to a certain extent, on the site of the growth, a peripheral tumour is likely to produce malignant pleural involvement whilst secondary inflammatory changes are uncommon, conversely, a main bronchus tumour is often complicated by secondary inflammatory lung changes so that pleural reaction is not infrequently inflammatory in origin The first symptom may be pain and the first sign a friction rub but these are on the whole uncommon It is more usual to find a pleural effusion with its accompanying symptoms and signs. A malignant effusion is often massive, bloodstained and recurs rapidly following aspiration. When malignant cells are being sought, it is advisable to remove a large quantity of fluid which is centrifuged and the deposit examined (see p. 147). In doubtful cases thoracoscopic inspection and biopsy of the pleura may provide a firm diagnosis Technically, the presence of a malignant pleural effusion does not

preclude surgical treatment with the removal of both the lung and the pleura; but the results of radical treatment have not been encouraging. Waterman, Domm and Rogers (1957) have, however, recently reported improvement following pleurectomy in such cases.

Invasion of the Chest Wall

The parietal pleura acts as a reasonably effective barrier to malignant invasion, but once this barrier is broken rapid invasion of the chest wall usually occurs, such invasion is almost always accompanied by severe pain and the presence of the latter should inevitably arouse suspicion. Radiographic changes in the rib or a palpable tumour are late findings but tenderness over the suspected area is an earlier and significant finding. A particular variety of chest wall invasion, causing the Pancoast syndrome, will be considered in detail later. Generally speaking, clinical and radiographic evidence of chest wall involvement will preclude resection; but in many instances the condition is only discovered at thoracotomy, and in these cases the block of involved chest wall can be removed if the affected area is not great. Occasionally a plastic or bony prosthesis is required to help stabilise the thoracic cage.

Invasion of the Mediastinum

The mediastinum may be involved either by direct invasion or by lymph node metastases and it is often difficult to distinguish the two. Involvement may be suspected either by the demonstration of a mediastinal mass or by secondary changes in the mediastinal structures. The former can often be demonstrated by radiographic means, particularly tomography and barium swallow. Those mediastinal structures most commonly involved are:

Oesophagus—Dysphagia with either pain or difficulty in swallowing is a relatively late symptom and it is more usual for oesophageal involvement to be demonstrated by a routine oesophagogram. It is often difficult to distinguish an oesophagus which is displaced by a potentially removable tumour from one that is actually invaded by tumour, so that, in practice, oesophageal changes alone are rarely regarded as sufficient to contra-indicate thoracotomy. In doubtful cases, an oesophagoscopy can be carried out at the same time as the bronchoscopy.

Phrenic Nerve Paralysis—Involvement of the phrenic with paralysis of the diaphragm is relatively common but does not constitute an absolute bar to resection. If the phrenic is involved in the lower part of the mediastinum where it lies on the pericardium, resection can readily include the affected strip of pericardium, but if the involvement is in the superior mediastinum it is almost certain that the superior vena cava or the aortic arch are involved and removal will not be possible.

Left Recurrent Laryngeal Nerve—A hoarse voice due to recurrent laryngeal nerve palsy is an occasional first symptom of bronchial carcinoma. It implies involvement of the nodes lying deep in the aortic arch and can be regarded as evidence of inoperability although it may still be possible to do a palliative resection in such cases.

Vena Cava—Vena caval obstruction by either the main growth or secondary nodes provides fairly conclusive evidence of inoperability. Technically it may be possible to excise and graft the involved vena cava, but this is in fact rarely practicable or justified.

Invasion of the Heart and Pericardium—Clinical evidence of cardiac involvement is provided by the occurrence of cardiac irregularities or a pericardial effusion (see p 200). Minor degrees of involvement are sometimes encountered at thoracotomy and resection of the involved area is often possible, but if involvement is suspected on clinical grounds, operation is not normally undertaken

Distant Metastases

Both blood-borne and lymphatic metastases may occur almost anywhere in the body (see p 140) but the following sites are commonly affected:

Cervical Lymph Nodes—The para-tracheal nodes on each side are continuous in the neck with the scalene nodes and the inferior deep cervical chain The scalene node is found lying deep to the clavicular and sternal heads of the sternomastoid muscle on the anterior scalene muscle It is most readily palpated by a bi-digital technique with index finger and thumb on either side of the sternomastoid muscle.

A palpably enlarged node can readily be removed for histological examination and the finding of malignant invasion rules out any prospect of radical lung resection although a palliative resection is still possible. Harken, Black, Clauss and Farrand (1954) advocated a routine and more extensive exploration of the scalene and upper mediastinal regions in all cases of cancer and have reported positive findings in nearly 40 per cent of 78 proven cases of lung cancer. They advise division of the sternomastoid muscle to gain access and use an illuminated laryngoscope as a retractor for the mediastinal exploration. The discovery of involved nodes will obviously influence the prognosis in all cases but, in many, will be a decisive factor in planning treatment

Umiker, DeWeese and Lawrence (1957) commenting on the distribution of the cancer in patients with positive scalene nodes mention that the majority are associated with upper lobe or main bronchus tumours and of eleven patients with peripheral type of tumour who had a scalene node biopsy, four were found positive. Both Umiker and Harken emphasize that a left lower lobe lesion may give rise to involvement of the right scalene node.

Harken's figure of 40 per cent is higher than one would expect from a study of the para-tracheal nodes in resected specimens. Nohl (1956) recorded involvement of para-tracheal nodes in 14 of 47 right-sided growths and in only one instance in 53 left-sided growths. It must be pointed out, however, that in Nohl's series para-tracheal nodes were not always available for examination.

In practice, diagnostic scalene node biopsy may have an important role to play but as a method of determining operability its routine use would appear to have only limited value

Liver—Early involvement of the liver is particularly difficult to determine.

The finding of tender nodules in an enlarged liver is a fairly late manifestation. A palpable liver, and particularly one that is slightly tender, arouses suspicion but does not, of itself, constitute evidence of involvement. In doubtful cases a laparotomy is justifiable, although even here small centrally placed deposits may not be revealed. Peritoneoscopy has only a limited use owing to the difficulties in making a complete inspection of the liver.

Brain—Cerebral metastases are relatively frequent. The occurrence of headaches, alterations in vision and alterations in behaviour and personality are the earliest manifestations and should be sought by direct questioning of both the patient and the relatives. The position is complicated by the not infrequent association of toxic psychoses and cerebral vascular disorders. In doubtful cases an electro-encephalogram may be helpful in demonstrating a localised lesion.

Bones—Secondary deposits in the bones also occur fairly commonly. The majority give rise to considerable pain which calls attention to their presence. If localised tenderness is elicited or a tumour palpable, a secondary deposit is almost certainly present. Difficulty often arises in connection with lumbar or sciatic pain, owing to the relative frequency of non-malignant lesions in this area. Distinction between the two is often impossible, but a history of previous sciatica would suggest a benign lesion and this diagnosis would be supported by a good response to immobilisation or physiotherapy; conversely, relief of pain by a short course of x-ray therapy suggests a malignant lesion but lack of response does not exclude it. X-ray changes in the bones occur late and radiography is therefore of little value when most required.

Other Considerations

Age

The influence of age on operability is bound up very largely with the assessment of the general condition of the patient. In the Brompton series there was a post-operative mortality of 9 per cent in patients below the age of 50 compared with 18 per cent for those who were 60 or more. Generally speaking, patients under the age of 60 can withstand a pneumonectomy without undue risk or grave disability, but over the age of 65 it is only those who are in good general condition who can be submitted to total removal of the lung. Less radical resections, however, are practicable even amongst those in the early seventies, but the risks in these older patients are somewhat increased. (See Table LII on p. 227.)

Other Pulmonary Conditions

The state of the lung that remains after resection is of considerable importance in assessing operability. Patients with generalized disease of the lungs with an already reduced function are unlikely to survive the loss of approximately half of the available lung tissue. Under these circumstances, other forms of treatment are to be preferred.

Chronic Bronchitis—Clinically, lung cancer seems particularly common amongst patients suffering from chronic bronchitis. The severe bronchitic with

persistent signs in the unaffected lung and radiographic changes is not an acceptable risk for resection Although resection may be safely and easily performed, the patient is likely to be severely crippled after the operation and survival as a 'respiratory cripple' would be intolerable. The matter, however, is complicated by the fact that many neoplasms tend to produce bronchitis or to aggravate a pre-existing bronchitis and occasionally the removal of a septic lung may have a beneficial effect upon the disability caused by the generalized disease For practical purposes, if it is found that intensive chemotherapy together with breathing exercises and antispasmodics will clear up a generalized bronchial infection, then resection is justified.

Emphysema—Generally speaking, emphysema tends to be associated with chronic bronchitis but often the changes of the former dominate the picture. In such patients, shortness of breath is a dominant symptom and this is associated with a fixed distended thorax with poor respiratory movements and weak breath sounds. Patients with the grosser forms of this condition are obviously unsuitable for surgical treatment, but the less severe cases are more difficult to assess. In such cases, detailed lung function studies may be helpful

Asthma—Mild asthmatics are not usually regarded as inoperable provided other factors favour resection. It is common experience that the presence of an infective lesion in the lung often aggravates an asthmatic condition and conversely its removal may give considerable relief. Asthmatic symptoms, however, usually tend to recur, though often as long as a year of freedom from attacks is obtained Severe asthmatics, however, are not accepted as the post-operative risks are high and the chances of improvement are small

Pulmonary Function Studies

It is obvious that after resection of a lung, the remaining lung must be adequate for the needs of the patient if he is to survive with reasonable comfort There seems little point in performing a technically successful pneumonectomy if the patient at the end of it is going to be severely restricted and incapacitated by shortness of breath Assessment of pulmonary function is therefore of paramount importance; but it is extremely difficult to determine the efficiency of one lung alone when both are present and the effects of the lung tumour and associated infection are operating The present commonly practised pulmonary function tests are relatively crude and do not give an accurate assessment in the doubtful cases Reliance is, therefore, usually placed on clinical details A rough guide to over-all function can be obtained from careful cross [illegible]
the onset of [illegible]
the appearar [illegible]
such as walking upstairs or walking and talking on the flat. In this way a very good guide to pulmonary function is obtained. Of the simpler functional tests, the maximum breathing capacity (M B C.) and the timed vital capacity (T V.C.) appear to be the most useful in ordinary cases. The former gives some idea of the capabilities of the lungs to ventilate and a reduction of the M B C below 50 per cent of normal would be regarded with suspicion The

T.V.C. gives some idea of the elasticity of the lung, normally about 75 per cent of a normal breath being expired during the first second of expiration In emphysema and lung fibrosis this percentage is considerably reduced: should it fall under 50 per cent, post-operative difficulties may be anticipated. Bronchospirometery enables one to determine the function of each individual lung separately; but this investigation has not been used extensively as the conditions under which it is performed are rather artificial and a clear-cut answer is usually not obtained in the border-line case where help is most required The development of the mass spectrometer and its use to determine the function of individual lobes under near normal conditions promises to be of considerable help in the future in surveying these difficult border-line cases (Fowler and Hugh Jones 1957)

Cardiovascular Disorders

The more serious forms of cardiovascular disease sufficient either to produce symptoms such as effort dyspnoea, fainting or angina, or to have caused a myocardial infarct are, of course, regarded as unfavourable findings Less severe conditions do not necessarily prove a bar to resection if other factors are favourable, even though the risks of surgery are somewhat greater

OPERATIVE SURGERY

With the full development of the standard pneumonectomy and a reduction of the operative mortality to below 10 per cent, surgical endeavour in the last few years has been directed along 3 lines —

(1) The development of more radical methods for removal of the growth and the lymph node area.

(2) Operations designed to conserve any healthy and uninvolved lung tissue (Lobectomy Sleeve Resection)

(3) Methods designed to improve the survival of those patients on whom complete removal of the growth and lymph nodes was not possible (Palliative Resection. Radioactive Gold Grains.)

Standard Pneumonectomy

This operation has been satisfactorily evolved during the last 15 years following the introduction of dissection techniques, recent improvements have been essentially those of detail In the majority, the lung containing the primary growth and any adherent parietal pleura is excised first, followed by the removal of paratracheal, subcarinal and paraoesophageal lymph nodes.

Aylwin (1951) recommended the early ligation of the pulmonary veins in order to avoid dislodging tumour cells into the circulation during mobilization of the lung He pointed out that 40 per cent of resected specimens show microscopic invasion of all coats of a pulmonary vein whilst macroscopic intraluminal polypoid masses are not uncommon The occasional occurrence of a massive tumour embolus of a cerebral vessel at the time of operation suggests that smaller and unsuspected emboli may occur more frequently.

Radical Pneumonectomy

Allison (1946) recommended the isolation and division of the pulmonary vessels within the pericardium as a means of increasing the margin between the growth and the operative section. This first step towards radical resection has been further developed by Brock and Whytehead (1955) who regarded it as a logical method of improving the survival rates based on sound surgical principles which have been generally accepted in the treatment of cancer elsewhere in the body. Their operation is described in detail in their paper, but essentially it involves a block dissection in one piece of the paratracheal nodes on both sides, the subcarinal nodes, a collar of pericardium around the hilum and the para-aortic nodes. The bronchus is divided at its origin from the trachea They recommended an extensive removal of the mediastinal nodes and surrounding areolar tissue including as much as possible from the opposite side of the mediastinum Although the operation is a more extensive one than the standard pneumonectomy, the operative mortality is claimed to be no higher.

Lobectomy

Peripheral tumours without involvement of the hilar nodes have for some time been treated by lobectomy and it has been found that not only has survival been equal to, or better than, that following pneumonectomy, but that the mode of survival has been happier. More recently, patients with a limited respiratory reserve have been deliberately treated by lobectomy with resection of hilar and mediastinal nodes because it was considered that they were unlikely to survive total lung removal The results in these cases were encouraging and of recent years a number of surgeons have been carrying out a lobectomy wherever it is possible to do so Belcher (1956) recently surveyed the results of this policy in 264 patients operated on during the preceding 6 years He found that approximately 50 per cent of 160 patients operated on 3 or 4 years before have survived. Bignall and Moon (1955) recorded a 3-year survival rate of 44 per cent compared with 38 per cent for pneumonectomy. They also comment on a significant difference in the operative mortality rates of the two groups Groups treated by pneumonectomy and lobectomy may show considerable differences in the types of tumour as well as in age and respiratory function. In my own series, for instance, 76 per cent of those treated by lobectomy had peripheral tumours, compared with only 25 per cent of those who had a pneumonectomy Although the two groups of cases are not strictly comparable there is, however, a suggestion that radical lobectomy, where practicable, offers as good a prospect of survival as pneumonectomy.

In addition, there is no doubt that patients on whom a lobectomy has been performed have much less subsequent disability than those in whom the whole lung has been removed Not only does the remaining lobe provide the patient with useful functioning lung tissue but it also helps to fill the pleural [illegible] From the point of view [illegible]

by extensive bronchial secretions: neither of these problems, however, is incapable of solution by careful post-operative handling By contrast, patients after pneumonectomy have a smoother post-operative course as far as chest complications are concerned. They are, however, more liable to cardiovascular disturbances, such as auricular fibrillation and to broncho-pleural fistulae and infection of the pleural cavity.

Sleeve Resection

An extension of the principle of conserving normal lung tissue has been advocated by Price Thomas (1956) who recommends excision of a portion of the main bronchus together with an involved lobe (sleeve resection) in those patients in whom the origin of the lobar bronchus is involved by growth Usually such a patient would be treated by pneumonectomy, but histological examination has indicated that involvement of the main bronchus is usually not extensive, whilst the remaining lobe is often normal. Resection of the greater part of the main bronchus for upper lobe tumours is readily carried out and the stem of the left lower lobe is sutured to the proximal stump of the main bronchus. A similar technique has been used in the treatment of lower lobe lesions and also in lesions involving the carina or lower trachea (Barclay, McSwan and Welsh 1957)

The post-operative course is little different from that of a standard lobectomy, and leakage at the suture line is an unusual complication

Palliative Resection

Approximately one patient in every five submitted for a resection is found to have a tumour which is unsuitable for removal These patients are either treated symptomatically after operation or given a post-operative course of irradiation The latter is, on the whole, not tolerated well by patients recovering from a thoracotomy and one is reluctant to have these patients return to hospital for several weeks after convalescence for treatment when their expectation of life is so poor The average survival after thoracotomy without resection in 53 of my own patients was 8 months and half were dead within 4 months

There are certain definite advantages in removing the primary tumour together with involved or infected lung in some patients with otherwise technically inoperable tumours Much malignant and infected tissue is thereby removed and some of the patients' most distressing symptoms (cough, sputum or haemoptysis) are relieved

Recently Abbey Smith (1957) has advised doing a palliative resection in all patients found to have a technically inoperable growth at thoracotomy In many instances in his series of 48 consecutive palliative operations (representing a resectability rate of 97 per cent) growth was left behind on the heart or great vessels The operative mortality was higher (20 per cent) in this group than in those undergoing a curative operation (9 per cent) The author regarded survival for at least 8 months with return to work as a worthwhile result and half of the survivors fall into this category He also noted that the final illness was long and unpleasant in only 3 of his patients; but more

Radical Pneumonectomy

Allison (1946) recommended the isolation and division of the pulmonary vessels within the pericardium as a means of increasing the margin between the growth and the operative section This first step towards radical resection has been further developed by Brock and Whytehead (1955) who regarded it as a logical method of improving the survival rates based on sound surgical principles which have been generally accepted in the treatment of cancer elsewhere in the body. Their operation is described in detail in their paper, but essentially it involves a block dissection in one piece of the paratracheal nodes on both sides, the subcarinal nodes, a collar of pericardium around the hilum and the para-aortic nodes. The bronchus is divided at its origin from the trachea. They recommended an extensive removal of the mediastinal nodes and surrounding areolar tissue including as much as possible from the opposite side of the mediastinum Although the operation is a more extensive one than the standard pneumonectomy, the operative mortality is claimed to be no higher

Lobectomy

Peripheral tumours without involvement of the hilar nodes have for some time been treated by lobectomy and it has been found that not only has survival been equal to, or better than, that following pneumonectomy, but that the mode of survival has been happier. More recently, patients with a limited respiratory reserve have been deliberately treated by lobectomy with resection of hilar and mediastinal nodes because it was considered that they were unlikely to survive total lung removal. The results in these cases were encouraging and of recent years a number of surgeons have been carrying out a lobectomy wherever it is possible to do so Belcher (1956) recently surveyed the results of this policy in 264 patients operated on during the preceding 6 years. He found that approximately 50 per cent of 160 patients operated on 3 or 4 years before have survived Bignall and Moon (1955) recorded a 3-year survival rate of 44 per cent compared with 38 per cent for pneumonectomy. They also comment on a significant difference in the operative mortality rates of the two groups. Groups treated by pneumonectomy and lobectomy may show considerable differences in the types of tumour as well as in age and respiratory function. In my own series, for instance, 76 per cent of those treated by lobectomy had peripheral tumours, compared with only 25 per cent of those who had a pneumonectomy Although the two groups of cases are not strictly comparable there is, however, a suggestion that radical lobectomy, where practicable, offers as good a prospect of survival as pneumonectomy.

In addition, there is no doubt that patients on whom a lobectomy has been performed have much less subsequent disability than those in whom the whole lung has been removed Not only does the remaining lobe provide the patient with useful functioning lung tissue but it also helps to fill the pleural cavity and prevent serious mediastinal displacement. From the point of view of the operation itself, lobectomy may provide more post-operative troubles The remaining lobe may be reluctant to expand and is not infrequently affected

by extensive bronchial secretions: neither of these problems, however, is incapable of solution by careful post-operative handling By contrast, patients after pneumonectomy have a smoother post-operative course as far as chest complications are concerned. They are, however, more liable to cardio-vascular disturbances, such as auricular fibrillation and to broncho-pleural fistulae and infection of the pleural cavity.

Sleeve Resection

An extension of the principle of conserving normal lung tissue has been advocated by Price Thomas (1956) who recommends excision of a portion of the main bronchus together with an involved lobe (sleeve resection) in those patients in whom the origin of the lobar bronchus is involved by growth Usually such a patient would be treated by pneumonectomy, but histological examination has indicated that involvement of the main bronchus is usually not extensive, whilst the remaining lobe is often normal. Resection of the greater part of the main bronchus for upper lobe tumours is readily carried out and the stem of the left lower lobe is sutured to the proximal stump of the main bronchus A similar technique has been used in the treatment of lower lobe lesions and also in lesions involving the carina or lower trachea (Barclay, McSwan and Welsh 1957)

The post-operative course is little different from that of a standard lobectomy, and leakage at the suture line is an unusual complication.

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details and widespread observations on the mode of death of patients treated by all the various methods are required before the significance of his findings can be fully evaluated

Resection of the Chest Wall

A small percentage of peripheral tumours tend to invade the parietal pleura and chest wall at a time when the disease has not spread to the mediastinum or elsewhere. These patients are otherwise operable and if the chest wall involvement is not extensive, operation is justified (Kirklin, McDonald, Clagett, Moersch and Gage 1955) The thoracotomy is performed away from the involved area if possible and the pneumonectomy and mediastinal dissection carried out before the involved chest wall is resected. The involved area is removed as a block with an adequate margin of normal tissue surrounding it. If necessary, some of the extrathoracic muscles will be removed as well. If the chest wall involvement is situated in the upper and posterior portions of the thorax, which are covered by the scapula and its muscles, little is required in the way of support; but if the involvement lies anteriorly in the relatively exposed region of the thoracic cage, a prosthesis is desirable to prevent undue paradoxical movement This can be done by either using the patient's own ribs as a bone graft, by employing boiled rib homografts or a plastic prosthesis The length of survival after resection of the chest wall has not been particularly encouraging but the relief of troublesome or incapacitating pain makes operation well worth while In patients with extensive chest wall invasion, a palliative resection of the primary growth can be performed followed by either implantation of radioactive gold grains into the remaining tumour, or post-operative conventional irradiation If pain is a prominent feature in these patients, multiple intercostal nerve division can be practised.

Pancoast Syndrome

The Pancoast syndrome is produced by a peripheral type of lung cancer [illegible] of the chest [illegible] The tumour [illegible] bodies of the second or third thoracic vertebrae, the lower trunk of the brachial plexus and the sympathetic chain This spread accounts for the classical syndrome of Pancoast, namely a Horner's syndrome with involvement of the lower trunk of the brachial plexus and rib erosion (see p. 199). The tumour is particularly unpleasant on account of the severe pain it produces By the time the syndrome is developed, the condition is technically inoperable and in the past, patients with this condition have been given radiotherapy; but the results have been disappointing and if the pain has been improved or relieved it has almost always recurred. Recently, in order to try to help these patients, bold surgical measures have been carried out aiming at removing the upper lobe with the tumour together with the involved upper ribs and the chest wall, and, if necessary, the involved part of the brachial plexus (Chardack and MacCallum 1956; Dontas 1957) Residual tumour can be treated with gold grains or radiotherapy.

Although survival after this operation has, in general, been short, a significant number of patients have been remarkably relieved, so that the policy appears to be justified.

Interstitial Irradiation

An alternative to palliative resection has recently been employed at the Brompton Hospital in conjunction with the Royal Marsden Hospital It

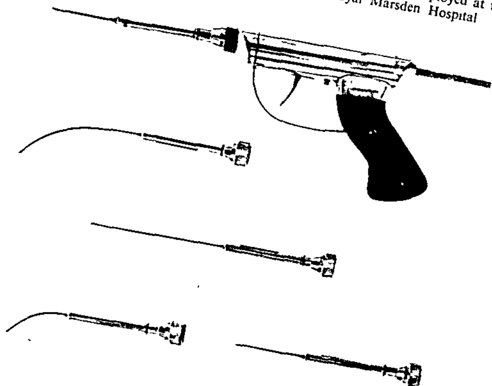


FIG 49

Gun for interstitial implantation of radioactive gold grains The newer type of fine needle is shown

consists of implanting radioactive gold grains into the tumour and any invaded lymph nodes at thoracotomy (Fig. 49) (see also p 241)

This method was developed at the Royal Marsden Hospital (Hodt, Sinclair and Smithers 1952) and has been used at many sites The technique is essentially similar to that of implanting radon seeds directly into the tumour Radon seeds, however, have some disadvantages They tend to vary in length so that it is difficult to use them in a precision instrument designed for multiple implantation; about seven days' notice is needed in ordering the seeds, almost

the entire cost of unused seeds has to be met if they are not used. To overcome these difficulties, the isotope of gold, ^{198}Au—prepared by irradiating pure gold in a nuclear reactor—is used. The sources (called grains to distinguish them from radon seeds) consist of gold wire sheathed in platinum, and have dimensions 2·5×0·8 mm. The half-life of ^{198}Au is 2·7 days, to be compared with that of radon, 3·8 days. 4·8 mc ^{198}Au deliver a radiation dose equal to that from 1 mc radon, and this activity can be produced in a few hours' irradiation The inactive sources are manufactured to a fine tolerance, and 15 are irradiated together in an aluminium magazine. Their activity can be rapidly measured without removing them from the magazine which can then be loaded into a specially designed 'gun' Unused sources can be re-irradiated Analysis shows that when 30 or more gold sources are used the cost is approximately the same as for radon seeds (at present about 7/– each), but that one-half to two-thirds of the cost is recovered if sources are not used.

This method has been used in three groups of patients with lung cancer:

(1) Those with a growth obviously irremovable due to extension into the mediastinum or involvement of lymph nodes (inoperable group)

(2) Those in whom a resection is performed but some malignant tissue is left behind (palliative resection)

(3) Those with technically operable growths in whom resection is not practicable owing to generalized bronchitis, emphysema or asthma (technically operable).

At operation an estimate is made of the volume of each tumour or lymph node to be implanted. From a table it is possible to determine the number of grains of the specific activity available which must be implanted to give the dose required Usually they are distributed as evenly as possible, but with tumours larger than 3 cm in diameter an attempt is made to implant two-thirds of the grains in the periphery and one-third in the central portion Tumour doses of from 6,000r to 10,000r are desirable. More than 60 grains are seldom used in one patient because extensive disease is unlikely to be effectively controlled for long, but large volumes may be implanted and many sources used A further development of this method involves the injection of gold grains into intrabronchial tumours at bronchoscopy. Ormerod (1937, 1953) demonstrated the value of radon seeds used in this way and reported successful recanalisation of the occluded bronchus. Although effective radiation of the whole tumour is unlikely by this means, it is a useful palliative measure for inoperable cases when the patient suffers from the effects of bronchial obstruction

Complications of Operation

Apart from those complications inherent in any thoracic operation, three conditions deserve special consideration:

Cardiac Disturbance

Multiple extra-systoles and auricular fibrillation are not uncommon complications of pneumonectomy, particularly in the more elderly patients

These complications are higher when an intrapericardial resection has been carried out. In many instances, the onset of auricular fibrillation passes almost unnoticed if tachycardia does not ensue, but in a proportion the rate is rapid and cardiac output falls. Hurt and Bates (1958) have suggested that the routine use of quinidine before and after operation reduces the incidence of fibrillation A test dose of 3 grains (0·19 g) is given several days before operation and if no reaction ensues, the patient is maintained on 3 grains three times a day. Others prefer digitalis, which can be either administered pre-operatively or started on the day following the operation Digitalis probably does little to prevent the onset of fibrillation but it will prevent a serious tachycardia should it occur If care is not exercised to prevent gross mediastinal displacement in either direction during the immediate post-operative period, the heart may be so displaced as to produce left ventricular failure and pulmonary oedema The development of an irritating cough with the expectoration of frothy sputum associated with sweating and hypotension points to this complication The diagnosis can be confirmed readily by determining the position of the trachea and apex beat; and the condition is rapidly relieved by immediately correcting the mediastinal displacement

Pulmonary Embolism

Pulmonary embolism was until recently an unusual complication of thoracic surgery; but of recent years increasing numbers of patients have developed this complication. This is perhaps the result of operating on older people or those with more extensive and less operable lesions The embolus is often a small one and not necessarily fatal, but massive and fatal emboli occur. The less severe cases are difficult to diagnose and are often regarded as coronary thromboses but this latter complication occurs only rarely The symptoms of the two conditions are similar; the onset is sudden with tightness or pain in the chest, tachycardia, hypotension and clinical shock The differentiation depends largely on the discovery of right ventricular over-action and the development of venous congestion An electrocardiograph will often help to distinguish the two conditions. Treatment is urgently required and is designed to maintain an adequate blood supply to the brain and coronary vessels and at the same time to prevent pulmonary arterial spasm and the development of secondary pulmonary thrombosis The patient is nursed flat and given oxygen and pethedine or morphia to relieve pain Aminophylline in doses of 0·24 to 0·48 g is administered Papaverine in doses of 0·1 mg may help to relieve pulmonary arterial spasm. Anticoagulants are started immediately using heparin and 'dindevan' Much can be done to prevent this complication by the routine use of anticoagulants and by getting the patient up soon after operation. 'Dindevan' can be given pre-operatively aimed to produce a prothrombin time of twice the normal figure at this level intravascular clotting is partly prevented but the clotting time is not increased Extensive bleeding at, or after the operation, is not encountered provided the prothrombin time does not rise above twice the control figure

Excessive Bronchial Secretions

Apart from the frothy secretions of pulmonary oedema due to cardio-vascular disturbances, excessive bronchial secretions due to traumatic or inflammatory causes are not infrequent after pulmonary resection. These are particularly common in patients suffering from chronic bronchitis and in those in whom there is much pulmonary sepsis. After any thoracic operation a certain amount of sputum is to be expected in the first few post-operative days; but it is only when this amount becomes excessive and cannot be expectorated completely by the patient's own efforts that action is required. In such cases, much can be done by the physiotherapist and the nursing staff, encouraging the patient to cough, whilst inhalations of Compound Benzoin Tincture (B.P.) and saline expectorants may help. If these measures do not adequately clear the bronchial tree or keep it clear, bronchoscopic aspiration is performed: this can be readily performed in the patient's bed in the ward provided a source of illumination for the bronchoscope and a powerful sucker are available. Bronchoscopy should be carried out with minimal local anaesthesia of the larynx alone so that the cough reflex is preserved. In more severe cases where repeated bronchoscopy might be required or where pulmonary ventilation is inadequate, a tracheostomy is done without delay: this again is a relatively simple procedure which can in an emergency be done in the ward, but it is better carried out under more ideal conditions in the operating theatre. It has the advantage of reducing the dead space air and making ventilation more efficient and also provides a ready channel for repeated aspirations of the tracheo-bronchial tree without undue trauma (Andrew 1956). Tracheostomy should not be left until the patient is *in extremis*, for probably by then irreversible changes will have occurred.

Results of Surgical Treatment

The majority of reports of the treatment of lung cancer have been concerned with the operative mortality and survival rates but little has been mentioned concerning the mode of survival. Attention is now being turned to this problem in the hope that the unhappy lot of some of the patients who have had a 'successful' resection may be improved.

Operative Mortality

At present the operative mortality is probably in the region of 10 per cent for all types of resection, but this figure naturally varies considerably with the type of patient being selected for surgery and the determination of the surgeon to remove the tumour. Abbey Smith (1957), for instance, deliberately aimed at removing the lung in every case submitted to operation and recorded a mortality rate of 20 per cent amongst those regarded as 'inoperable' by the criteria generally applied.

The mortality is higher after pneumonectomy than lobectomy (Churchill, Sweet, Soutter and Scannell 1955; Sellors 1955; Bignall and Moon 1955; Gifford and Waddington 1957) (Table LII). It increases with age; thus

Ochsner, Ray and Acree (1954) recorded 14 per cent mortality among patients under 50 years old and 24 per cent among those aged 60 to 69; whilst Bignall and Moon (1955) found a rate of 7 per cent rising to 13 per cent. Gifford and Waddington (1957) found a higher mortality after right-sided operations, both pneumonectomies and lobectomies Deaths from 'cardio-pulmonary failure' accounted for 24 per cent of deaths after right pneumonectomy and only 10 per cent after left pneumonectomy; the corresponding figures for lobectomy were 12 per cent and 2 per cent. In the Brompton series between 1940 and 1955

TABLE LII

Post-operative Mortality (Death Within 2 Months of Operation) in 599 Patients Treated Surgically Between 1940 and 1955 (Brompton Hospital)

		Total patients	*Post-operative deaths*	
			Number	*Per cent*
Total		599	78	13
Age (years)*	*Under 50*	150	14	9
	50–59	290	35	12
	60 or more	158	29	18
Sex	*Men*	547	72	13
	Women	52	6	(12)
Operation	*Pneumonectomy*	480	67	14
	Lobectomy	119	11	9
Side	*Right*	311	50	16
	Left	288	28	10

* 1 patient's age was not recorded
Percentage in brackets is based on less than 100 cases

there was also a higher death rate after right-sided pneumonectomies (20 per cent of 212 on the right; 12 per cent of 198 on the left) but the rates in the lobectomies were almost the same (6 patients out of 55 on the right and 5 out of 45 on the left).

A better understanding of the problems of the post-operative period, particularly the recognition of pulmonary embolism and the management of excessive secretions by tracheostomy has helped to reduce post-operative mortality from the high figures recorded in the early reports

Survival

The 5-year survival rate of all patients operated on will, of course, be influenced by the operative mortality Reports based on operations done when this mortality was much higher than at present will, therefore, give lower figures than might reasonably be expected now Ochsner, Ray and Acree (1954) recorded only 13 per cent of 229 resections and Churchill, Sweet, Soutter and Scannell (1950) 12 per cent of 48 pneumonectomies and 19 per cent of 21

lobectomies. Price Thomas (1952) and Sellors (1955) both found 5-year rates of 21 per cent. Bignall and Moon (1955), assuming an operative mortality of 10 per cent, suggested that 40 per cent of all who had a resection might survive 2 years and 30 per cent 5 years. *In the Brompton series of 521 patients* who survived 2 months or longer the crude survival rates were 50 per cent for 2 years and 27 per cent for 5 years (Table LIII).

TABLE LIII

The Survival Rates (1 year and 5 years) of Patients who Lived 2 Months or Longer After Resection (Brompton Hospital, 1940 to 1955)

	1 year			5 years		
	Total 'at risk'	Survived		Total 'at risk'	Survived	
		Number	Per cent		Number	Per cent
Total	521	347	66	221	75	34
Age (years) *Under 50*	136	94	69	77	28	(36)
50–59	255	167	65	101	34	34
60 or over	129	86	67	43	13	(30)
Sex *Men*	475	316	67	201	66	33
Women	46	31	(67)	20	9	(45)
Operation *Pneumonectomy*	413	263	64	198	64	32
Lobectomy	108	84	78	23	11	(48)
Histological type						
Squamous	263	193	73	118	50	42
Undifferentiated	193	103	53	74	16	(22)
Adenocarcinoma	49	42	(86)	18	7	(39)
Site *Right lung*	261	175	67	106	39	37
Left lung	260	172	66	115	36	31
R upper lobe	102	70	69	35	14	(40)
L upper lobe	148	101	68	62	22	(35)
R lower lobe	125	86	69	59	20	(34)
L lower lobe	95	60	(63)	47	12	(26)

Percentages in brackets are based on less than 100 cases

The poorer prognosis of undifferentiated tumours is well known (McDonald, McBurney, Carlisle and Patton 1951; Borrie 1952; Kirklin, McDonald, Clagett, Moersch and Gage 1955; Gifford and Waddington 1957). The considerable influence of metastases in the regional nodes is also well established (Overholt and Schmidt 1949; Churchill, Sweet, Soutter and Scannell 1950; Moore 1951, Carlisle, McDonald and Harrington 1951; Thompson 1952; Borrie 1952, Ochsner, Ray and Acree 1954; Bignall and Moon 1955; Gifford and Waddington 1957)

Collier, Blakemore, Kyle, Enterline, Kirby and Johnson (1957) studied the relationship of survival to microscopic evidence of vascular invasion by

the tumour. Such invasion appeared to have a greater influence than node metastases. Thus, 6 of 10 patients with node involvement but no vascular invasion lived 5 years compared with only 2 of 26 in whom there was evidence of vascular invasion but no node involvement. This result did not appear to be merely a reflection of the histological type of tumour within the groups, for similar differences were seen when only squamous cancers were considered.

Carlisle, McDonald and Harrington (1951), from a study of 68 patients with squamous tumours at the Mayo Clinic, concluded that the prognosis was worse with tumours of the left lung. Borrie (1952) suggested it might be better with upper lobe lesions, and Bignall and Moon (1955) found higher survival rates after resection of upper lobe cancers, the differences between the right and left sides appearing to be largely due to low survival rates with tumours of the left lower lobe. In the series of Gifford and Waddington (1957), although those with left lower lobe lesions had the highest incidence of node involvement, the survival rate among them was similar at 5 years to that of patients with left upper lobe cancer, however, the 2-year rates were lower. In the Brompton series (which includes some of the cases reported by Bignall and Moon) the left lower lobe group also had the lowest survival rates (Table LIII). It seems likely, therefore, that the survival rate is influenced by the site of the tumours, right-sided lesions leading to a higher operative mortality and lesions of the left lower lobe to a lower survival rate (see p. 190).

The number of operations in women is still too small for reliable comparison of their survival rates with those experienced by the men. Comparison is invalid unless allowances can be made for differences of histological types, and division according to type leads to very small sub-groups. Bignall and Moon reported 41 women and 412 men with 2- and 5-year rates of 65 per cent and 57 per cent in the women and 46 per cent and 31 per cent in the men. Gifford and Waddington found 2- and 5-year rates of 38 per cent and 25 per cent for 29 women and 45 per cent and 29 per cent for 318 men. In the Brompton series the corresponding rates were 47 per cent and 32 per cent for women and 50 per cent and 27 per cent for men. The differences are too small to conclude that the prognosis is worse in women.

The greatest post-operative mortality occurs within the first 6 months of operation and this is probably caused by the deaths of patients who had already developed undetected secondary deposits at the time of operation. Recurrence in the stump of the bronchus after resection is uncommon, particularly when one considers the narrowness of the margin of normal tissue at the level of bronchial section. Recurrence in mediastinal nodes is more common, and in this connection recurrence in the right paratracheal nodes after left-sided resections is worthy of note. Nohl (1957) has indicated that left-sided tumours frequently spread to the right side in this way (see p. 137). Of the distant metastases which account for the majority of the later deaths, special mention should be made of cerebral involvement. This appears to be higher in the operative series than in those treated by other means or not treated at all suggesting that tumour emboli are dislodged at the time of operation. Aylwin (1951) has suggested that early control of the pulmonary veins

may help to prevent this occurrence. Collis (1944) has pointed out that the brain is particularly vulnerable if either tumour or infected emboli are dislodged from the lung. He considers that many of these emboli reach the brain through the paravertebral venous plexus

Mode of Survival

A careful survey of patients surviving pneumonectomy and lobectomy will leave a sense of dissatisfaction regarding the quality of survival in some of the patients; although the tumour has apparently been successfully eradicated, residual symptoms and disabilities make life miserable and occasionally intolerable. *The causes of this are being investigated in the hope that future* trouble may be avoided The most troublesome phenomena are:

Dyspnoea—Shortness of breath after operation is primarily an indication that the remaining lung is not adequate to meet the needs of the patient and suggests, in fact, that the operation was not really justified. This reflects, of course, on the assessment of operability, and the difficulties of judging lung function have already been mentioned. There are two factors, however, which may aggravate the existing pulmonary insufficiency. Mediastinal displacement of the considerable degree necessary to fill the space left by the removed lung inevitably produces over-expansion of the remaining lung. If this lung is relatively normal, such over-expansion has little effect on its function, but if emphysematous changes are already present these may be aggravated. McIlroy and Bates (1956) have demonstrated these changes by physiological means It would appear that extensive mediastinal displacement should be prevented in patients liable to become dyspnoeic. This can be carried out by a thoracoplasty performed as a second operation several weeks after the resection, or by filling the residual space with a plastic prosthesis, also several weeks after the resection. Neither of these operations is recommended at the time of the resection The addition of a thoracoplasty to a resection makes the operative procedure too formidable, whereas the use of a prosthesis at the time is more likely to be followed by infection than if it is used later. In addition, 2 to 3 weeks of observation after operation are advisable in order to get a better idea of the problems involved. It is only in those patients who are moderately dyspnoeic and who are still left with a large space after 3 weeks that action is required. Patients treated in this way are being carefully followed up particularly with regard to lung function, but it is too early yet to determine whether the results justify the procedure.

Chronic Bronchitis—Sufferers from chronic bronchitis are much more liable to develop troublesome dyspnoea in the later post-operative period and it is this group particularly which causes considerable concern Many bronchitics can be reasonably well controlled by chemotherapy, antispasmodics, breathing exercises and protection from fog and smoke; but others prove quite intractable Pre-operatively favourable cases can be controlled by antibiotics and antispasmodics but if these are ineffective operation should only be undertaken under special circumstances. (It is in such patients that one *should try to provide alternative treatment if practicable.)*

Mediastinal Displacement—Apart from the effects on the opposite lung, moderate or severe mediastinal displacement combined with an extensive fibrothorax and frozen chest on the affected side, produce a certain amount of discomfort: this may take the form of tightness or heaviness in the chest to which the patient can readily become accustomed, but in a proportion of patients this discomfort becomes severe and intolerable. How much of this is due to mediastinal displacement and how much to the development of fibrous tissue is not clearly understood, but both thoracoplasty and prostheses may perhaps help to reduce this disability. Another important aspect which has a decided bearing on these phenomena relates to one of the advantages of doing a lobectomy. In these cases the remaining lobe will expand to help fill the residual space left after resection. Mediastinal displacement is thus minimised and an excessive fibrosis of the chest is avoided. There is little doubt that patients who have had a lobectomy are much less disturbed and have a far better post-operative course than those who have had a pneumonectomy This, by itself, provides a powerful argument in favour of conservative resection of the lung

Late Post-operative Pain—This is perhaps one of the most difficult and distressing of the post-operative complications. Occasionally, severe pain is due to recurrence of the tumour with invasion of the chest wall or spine, but more often it is more directly connected with the thoracotomy than with the tumour. The condition is commoner in men than women and in the elderly as opposed to the younger, and thin people are more prone to it than fat The management of the intercostal nerve bundle at the time of operation does not appear to play an important part in the development of this phenomenon This does not mean that careful attention should not be paid to these structures at [illegible]

from routine physiotherapy or intercostal injections of long-acting analgesics or alcohol Multiple intercostal nerve section, cordotomy and leucotomy have been carried out from time to time but the results are not encouraging

CONCLUSION

The present status of surgery in the treatment of lung cancer is by no means an entirely happy one In favourable patients there is a 25 to 30 per cent chance of survival for 5 years but this figure has not advanced significantly in spite of obvious and definite improvements in surgical technique It seems unlikely that further significant technical improvements will be forthcoming, nor can it be supposed that they will materially improve matters should they come

Surgical endeavour is at present pursuing two other avenues one aims at combining an effective excision of the tumour and lymph nodes whilst at the same time conserving as much uninvolved lung tissue as possible, whilst the other is concentrating on improving the outlook for those considered unsuitable for radical resection.

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A careful survey of patients surviving pneumonectomy and lobectomy will leave a sense of dissatisfaction regarding the quality of survival in some of the patients; although the tumour has apparently been successfully eradicated, residual symptoms and disabilities make life miserable and occasionally intolerable. The causes of this are being investigated in the hope that future trouble may be avoided The most troublesome phenomena are:

Dyspnoea—Shortness of breath after operation is primarily an indication that the remaining lung is not adequate to meet the needs of the patient and suggests, in fact, that the operation was not really justified. This reflects, of course, on the assessment of operability, and the difficulties of judging lung function have already been mentioned. There are two factors, however, which may aggravate the existing pulmonary insufficiency. Mediastinal displacement of the considerable degree necessary to fill the space left by the removed lung inevitably produces over-expansion of the remaining lung. If this lung is relatively normal, such over-expansion has little effect on its function, but if emphysematous changes are already present these may be aggravated McIlroy and Bates (1956) have demonstrated these changes by physiological means. It would appear that extensive mediastinal displacement should be prevented in patients liable to become dyspnoeic This can be carried out by a thoracoplasty performed as a second operation several weeks after the resection, or by filling the residual space with a plastic prosthesis, also several weeks after the resection. Neither of these operations is recommended at the time of the resection The addition of a thoracoplasty to a resection makes the operative procedure too formidable, whereas the use of a prosthesis at the time is more likely to be followed by infection than if it is used later. In addition, 2 to 3 weeks of observation after operation are advisable in order to get a better idea of the problems involved. It is only in those patients who are moderately dyspnoeic and who are still left with a large space after 3 weeks that action is required Patients treated in this way are being carefully followed up particularly with regard to lung function, but it is too early yet to determine whether the results justify the procedure.

Chronic Bronchitis—Sufferers from chronic bronchitis are much more liable to develop troublesome dyspnoea in the later post-operative period and it is this group particularly which causes considerable concern Many bronchitics can be reasonably well controlled by chemotherapy, antispasmodics, breathing exercises and protection from fog and smoke; but others prove quite intractable. Pre-operatively favourable cases can be controlled by antibiotics and antispasmodics but if these are ineffective operation should only be undertaken under special circumstances (It is in such patients that one should try to provide alternative treatment if practicable.)

Mediastinal Displacement—Apart from the effects on the opposite lung, moderate or severe mediastinal displacement combined with an extensive fibrothorax and frozen chest on the affected side, produce a certain amount of discomfort· this may take the form of tightness or heaviness in the chest to which the patient can readily become accustomed, but in a proportion of patients this discomfort becomes severe and intolerable How much of this is due to mediastinal displacement and how much to the development of fibrous tissue is not clearly understood, but both thoracoplasty and prostheses may perhaps help to reduce this disability Another important aspect which has a decided bearing on these phenomena relates to one of the advantages of doing a lobectomy In these cases the remaining lobe will expand to help fill the residual space left after resection. Mediastinal displacement is thus minimised and an excessive fibrosis of the chest is avoided. There is little doubt that patients who have had a lobectomy are much less disturbed and have a far better post-operative course than those who have had a pneumonectomy. This, by itself, provides a powerful argument in favour of conservative resection of the lung

Late Post-operative Pain—This is perhaps one of the most difficult and distressing of the post-operative complications Occasionally, severe pain is due to recurrence of the tumour with invasion of the chest wall or spine, but more often it is more directly connected with the thoracotomy than with the tumour. The condition is commoner in men than women and in the elderly as opposed to the younger, and thin people are more prone to it than fat The management of the intercostal nerve bundle at the time of operation does not appear to play an important part in the development of this phenomenon This does not mean that careful attention should not be paid to these structures at the time of operation It would appear more likely that the intercostal nerves are caught up and strangled by the fibrosis which develops after pneumonectomy The condition is extremely difficult to treat, but sometimes relief can be obtained from routine physiotherapy or intercostal injections of long-acting analgesics or alcohol. Multiple intercostal nerve section, cordotomy and leucotomy have been carried out from time to time but the results are not encouraging

Conclusion

The present status of surgery in the treatment of lung cancer is by no means an entirely happy one. In favourable patients there is a 25 to 30 per cent chance of survival for 5 years but this figure has not advanced significantly in spite of obvious and definite improvements in surgical technique It seems unlikely that further significant technical improvements will be forthcoming, nor can it be supposed that they will materially improve matters should they come

Surgical endeavour is at present pursuing two other avenues: one aims at combining an effective excision of the tumour and lymph nodes whilst at the same time conserving as much uninvolved lung tissue as possible, whilst the other is concentrating on improving the outlook for those considered unsuitable for radical resection.

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CHAPTER XXII

RADIOTHERAPY

D. W. SMITHERS

INTRODUCTION

OF the very large number of patients with bronchial carcinoma who come to hospital, only a small proportion are curable by any of the present treatment methods. Chemotherapy alone attempts to deal with the disseminated disease. It may succeed in modifying its course for a short time (see Chapter XXIII), but has, so far at least, been quite ineffective as a means of cure. Surgery and radiotherapy in varying degrees are both of proved effectiveness in complete tumour eradication under favourable circumstances, but are both local in their action. Although they may succeed even when spread has taken place to the lymph nodes within the thorax, they make no attempt to control blood-borne metastases Differential absorption of radioactive isotopes in tumour tissues—the only known radiotherapy method which has been effective in dealing with widely disseminated cancer—so far offers no real prospect of future success in this disease.

Of the patients with bronchial carcinoma seen in hospital, over 60 per cent have undifferentiated tumours which have such a high rate of dissemination by the blood stream that over 80 per cent have metastasised by this route before death (Galluzzi and Payne 1955) Even with squamous-cell tumours, which *form rather less than 25 per cent of the total seen, metastases* occur before death in over 40 per cent Since many of these patients are, in addition, old and feeble, it is probable that less than 20 per cent of those reporting to hospital at the present time with bronchial carcinoma have any prospect of cure at all by either of the local treatment methods available Without a dramatic advance in detection leading to earlier and frequently pre-symptomatic diagnosis, a change in the natural history of the disease, or the discovery of a means of dealing with disseminated tumour cells, no great change in cure rate for this disease can be expected. A radical change in the proportion diagnosed at an early stage, though seemingly unlikely at present, would appear to be much [illegible] method of prevention of a [illegible] m. [illegible] ed, a fair prospect of cure already exists; so long as they come to treatment after their tumours have metastasised, nothing more than some useful palliation can at present be expected.

RADIOTHERAPY METHODS

Most radiotherapy for bronchial carcinoma is given with x-ray beams Such treatment—in which the beam first passes through a considerable thickness

of normal tissue—requires special apparatus and much care in planning if it is to have any chance of success in any but the most unusual case of high radiosensitivity with a well localised tumour. Some success has, nevertheless, been achieved in the past by the use of carefully planned and accurately directed multiple small field therapy or its extension to rotation treatment in a few patients inoperable because of the situation of the tumour, of intercurrent disease, or of refusal of surgery, rather than because of spread The advent of supervoltage x-ray apparatus and the equivalent telecurie units, has made it possible, for the first time, consistently to deliver effective tumour doses at a depth without severe local or general reactions in the normal tissues Their mere availability does not, however, increase the number of patients with less advanced disease referred for treatment. They have only been in use in this country for any quantity of patients with bronchial carcinoma during the past 6 or 7 years, a period during which energetic attempts were being made to resect a larger proportion of involved lungs. Supervoltage x-rays have, therefore, been used almost exclusively for patients with advanced disease, moreover, with the rising resection rate, they are in fact being employed in an even more unfavourable group of cases than was submitted to radiotherapy before

Tumour implantation with radon seeds has been practised via the bronchoscope for a number of years and bronchoscopic tumour infiltration with radioactive colloidal gold has recently been tried, but these methods by this route can hardly be expected to deal adequately with the primary tumour except on rare occasions and do not attempt to deal with lymphatic spread Implantation of radioactive isotopes at thoracotomy presents a better prospect of achieving some success, at least in theory, and is now undergoing trial

The injection of radioactive particles into the affected bronchus or into the artery supplying the lobe involved, in the hope of differential absorption in the tumour and invaded lymphatics, has recently been tried and is an interesting experimental method without, as yet, much practical value The injection of radioactive colloidal solutions into the pleural cavity in cases of effusion due to tumour spread has proved to be a useful means of palliation

RADICAL TREATMENT AIMED AT CURE

Attempts to use external irradiation for eradication of the disease may be made alone or in combination with surgery. Since such a small proportion of patients with this disease have, by the time they reach hospital, any chance at present of cure by any local method of treatment, and since it is the general practice to treat this group by surgery alone, there is still little evidence to indicate what radiotherapy might achieve.

Pre-operative X-ray Treatment

At the Medical Research Council Radiotherapeutic Research Unit at Hammersmith Hospital a test of the value of pre-operative irradiation was carried out (Bromley and Szur 1955). Between November 1949 and October

1953 all patients judged to have removable tumours or tumours irremovable solely because of their situation, were treated by irradiation and reassessed for surgery after a period of convalescence—the number of such patients is not stated. If, on clinical, radiological and bronchoscopic findings, they were again judged operable, they were advised to have a thoracotomy. The average time between first attendance at the clinic and operations was 19 weeks. Sixty-six patients eventually had a resection performed following irradiation. Histological confirmation of the diagnosis had been obtained in all cases before treatment. The histological type was squamous cell carcinoma in 42, undifferentiated carcinoma in 11, adenocarcinoma in 3, and there were 10 others. In 29 patients (44 per cent) no residual tumour was found in the primary site or in the regional lymph nodes; in 14 (21 per cent) there was evidence of some degenerate tumour cells present, in 19 (29 per cent) there was residual tumour with what appeared to be viable cells; and in 4 cases (6 per cent) the specimen was lost. Ten patients died post-operatively (6 squamous-celled, 3 undifferentiated, 1 other), five of them being patients with no residual tumour in the lung and one with only degenerate tumour cells. Seven of the 13 patients still alive at the time of the report had no tumour present at resection, two being alive over five years after treatment. Thirteen, at least, of this group seem, therefore, to have had an unnecessary operation. Further, this operation seems to have been the cause of death in six of these patients. There was a high incidence of broncho-pleural fistula (13) and of empyema without fistula (5), both serious complications of this method of treatment, one or other occurring in 27 per cent of the total. Fistula was a fatal complication in all cases except one. It was not considered that the method of treatment had produced impressive results (Table LIV). It had, however, demonstrated that in an operable group of cases, where the patients remained well and

TABLE LIV

Pre-operative X-ray Treatment for Carcinoma of the Bronchus
(Adapted from Bromley and Szur 1955)
Hammersmith Hospital, London

Pre-operative irradiation + resection, 66

	No residual tumour	Degenerate cells only	Residual viable cells	Specimen lost
	29 (44%)	14 (21%)	19 (29%)	4 (6%)
Died post-operatively 10	5	1	2	2
Still alive in 1955, 13 (2>5 yrs)	7	2	3	1

Possibly unnecessary operation with 6 deaths: 15 (23%)   Necessary operation: 6 (9%)



Fig. 50

Male, aged 64, with undifferentiated carcinoma treated by x-rays in November 1944 Radiographs before (A), and 10 years after treatment (B) Patient alive and well for 12 years following irradiation

without evidence of distant spread following irradiation long enough to be operated on, over 40 per cent—and possibly 65 per cent—of these tumours could be eradicated from the chest by radiotherapy alone, as judged by histological examination of the primary site and nodes, even when using poor quality (250 kV) x-rays.

X-ray Therapy Alone

That a few patients with bronchial carcinoma survive for considerable periods following irradiation has long been known Leddy and Moersch (1940) treated 125 patients and (as a control) observed another 125 who were left untreated, all these patients had histological confirmation of the diagnosis Five of the treated patients lived over 5 years (one living 12 years) and all those left untreated died within a year. Paterson, Tod and Russell (1950) reported 7 five-year survivors, and Hilton (1955) 8 Many other isolated cases could be quoted Since an occasional patient may live some years without any treatment (6 years from the time a piece was first obtained for biopsy in one of our cases) and since the diagnosis of bronchial carcinoma is particularly prone to error—at times even with a positive biopsy report (Smithers 1953)—it is hardly surprising that some of those recorded as successfully treated by radiotherapy have been discounted Table LV shows a group of long survivors treated at the Royal Marsden Hospital from which all doubtful cases have been omitted. Figure 50 shows the radiographs of the patient treated in 1944, who

TABLE LV

Survival for More than Five Years Following Radical X-ray Therapy for Patients with Carcinoma of the Bronchus
Royal Marsden Hospital, London

Year of treatment	*Number of patients living more than 5 years*	*Histological type*	*Survival*
1939	1	Not known	Died with multiple metastases 7 years later
1940	1	Squamous-cell	Died of intercurrent disease with no sign of recurrence 14 years later
1944	1	Undifferentiated	*Alive and well 12 years later*
1946	1	Not known	Died with multiple metastases 8 years later
1947	2	Squamous-cell	Alive and well 9 years later
		Not known	Inoperable at thoracotomy; alive and well 9 years later
1948	1	Squamous-cell	Alive and well 8 years later
1949	1	*Undifferentiated	Alive and well 7 years later
1950	1	Squamous-cell	Alive and well 7 years later

* This patient had a pneumonectomy following irradiation but no residual tumour was found on histological examination

was still alive 12 years after treatment. Table LVI contains particulars of 7 patients who died following irradiation but who had no residual tumour locally in the lung on post-mortem examination. These reports of a number of genuine bronchial carcinomas with satisfactory local response to irradiation are

TABLE LVI

Some Patients Dying After X-ray Treatment for Bronchial Carcinoma in whom No Residual Primary Tumour was Found at Necropsy
Royal Marsden Hospital, London

Age of patient	*Histological type of carcinoma*	*Cause of death*	*Interval after treatment to death (months)*
19	Undifferentiated	Metastases	4
26	Undifferentiated	Metastases	8
30	Undifferentiated	Metastases	9
47	Undifferentiated	Metastases	4
50	Squamous and undifferentiated	Metastases and carcinoma of the kidney	10
53	Undifferentiated	Metastases	3
68	Squamous	*Coronary thrombosis*	2

of greater significance than would at first sight appear, since they were taken from those most unpromising groups of patients rejected as unsuitable for surgery in which the possible cure rate by any local treatment method is extremely low and by surgery is nil

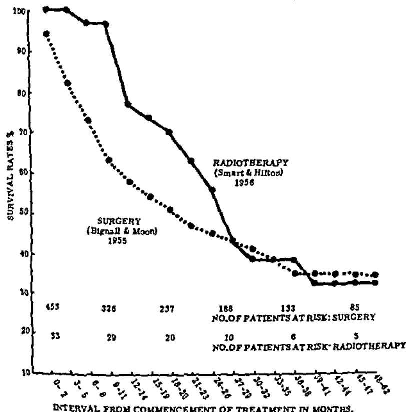


Fig 51

Carcinoma of the bronchus Survival of patients with operable tumours following surgery and radiotherapy (10 per cent operative mortality omitted from surgical figures, no immediate radiotherapy mortality)

Recently Smart and Hilton (1956) have reported the preliminary assessment of a most interesting experiment in the treatment of patients with operable bronchial carcinoma by external irradiation alone. The first 33 of these patients treated by them (19 squamous cell carcinomas 6 undifferentiated carcinomas, 8 without histological classification but with tumour cells in the sputum) included 12 followed for 5 years or more. Four of these were alive and well

(3 squamous cell, 1 undifferentiated), which is 33 per cent, a rate equivalent to that obtained with surgery, although the series is much too small for confident comparison. When Smart and Hilton compared the survival rates at 2-monthly intervals with the surgical results reported by Bignall and Moon (1955) the radiotherapy figures appeared rather better than those for surgery over the first two years and much the same thereafter (Fig 51). Since 10 per cent of



Fig 52

^{192}Iridium implant into bronchial carcinoma.
(By courtesy of Dr U K Henschke, Memorial Hospital, New York)

the surgically treated patients had died within two months of operation and had been excluded on that account, the radiotherapy result up to two years in this small series was actually an improvement on the surgical figures, 56 per cent surviving for that period against 42 per cent. The surgical series also excluded those found to be inoperable at thoracotomy. We have yet to see reports of operable cases treated by supervoltage x-rays or telecurie units It must be remembered, however, that supervoltage irradiation cannot be expected to improve the survival rate in late cases with dissemination; it will have to be evaluated as a curative method of treatment in early, operable cases, since these are the only ones providing a real opportunity for success with any local treatment

Some work has been done on the use of grid therapy irradiation for bronchial carcinoma (Harris 1952; Marks 1952). Here, the equivalent of multiple small beams is used and very high local tumour doses are given to parts of the tumour, with low doses in other tumour regions. There is n[illegible] firm evidence in favour of this method for these particular tumours at pres[illegible]

Implantation of Radioactive Sources

Another attempt to extend the chance of cure by radiotherapy has been made. This is by the use of small radioactive sources for implantation at thoracotomy in patients judged clinically to be operable but in whom, when the chest is opened, removal of all the tumour and nodes proves to be impracticable. This treatment method using radon seeds has been practised by Henschke (1957) since 1941. Up to 1955 he had treated 108 patients, with 12 living one year or more, 8 for two years or more, and 1 still alive at 4 years and 8 months During 1956 and 1957 he employed radioactive iridium (^{192}Ir) sources sometimes spaced in nylon tubing, with a number of technical and economic advantages (Fig 52) An implant method using gold grains was evolved by Hodt, Sinclair and Smithers (1952) and advocated for use in this way with bronchial carcinoma by Smithers (1955). It has been carried out by Sir Clement Price Thomas, Mr N R. Barrett, and Mr W. P Cleland (see Chapter XXI) In the locally advanced group of cases for which it is employed, only a limited success can be expected, but useful tumour regression has already been obtained (Fig. 53). The potential value of these methods is that they may extend the range of curability in patients found inoperable at thoracotomy, their immediate practical value is that they produce some palliation and these patients do not have a major operation performed, with all its risks, strain and expense, without anything being done which might favourably affect the course of their disease.

The Future of Radiotherapy for Operable Bronchial Carcinoma

The curative potential of radiotherapy for bronchial carcinoma has still to be determined. *Once symptoms have appeared, it cannot as yet,* on the slender evidence available, be confidently dismissed as being certainly inferior to surgery. It should be awarded a place in the treatment of a selection of the

more hopeful cases on any unbiased assessment of its value at the present time Further trial, under the best possible conditions, using supervoltage irradiation, is clearly needed. The limit on progress in curative therapy is set at present by the nature and spread of the disease at the time the patients come for treatment. The unassailable field for surgery lies in the treatment of early bronchial carcinoma with the suspicious, symptomless and sometimes undiagnosed tumour, which on resection proves to be malignant. The particular value of radiotherapy for some of the less advanced cases would seem to lie with those patients inoperable becuase of tumour situation only, with a few of the doubtfully operable group, with some of the older patients, and with the



Fig. 53

Female, aged 51, with inoperable carcinoma of the bronchus (A), and (B) showing disappearance of right hilar mass after insertion of gold grains 2½ months previously.

more undifferentiated tumours. Further experience with supervoltage irradiation in these cases should lead to firmer judgment on the future of radiotherapy as a curative method in bronchial carcinoma. This is only likely to happen if the results achieved in all patients seen, however treated, are assessed together. A joint attempt by surgeons and radiotherapists should be made to improve the prospects for those comparatively few patients with bronchial carcinoma in whom there is any chance of success at all by the use of local therapy. Attempts to get more patients to hospital while the disease is still treatable have not yet been sufficiently energetic and are at present far more likely to improve the results than anything else.

Palliation

General Considerations

Nearly all reports on radiotherapy in bronchial carcinoma deal with inoperable cases where palliation is the aim and any considerable prolongation of life, except in an occasional case, is not to be expected The effect of radiotherapy on survival in some of these cases has been studied by many authors, more recently by Garland and Sisson (1956) in America, and by Bignall (1956) in this country. Bignall examined the records of inoperable patients not known to have had extrathoracic metastases when first seen The survival times were compared in these patients with and without x-ray treatment Some increase in life span was found following irradiation but it was unlikely that this was as much as 10 per cent in the proportion surviving 1 year from diagnosis, or 5 per cent in those surviving 2 years. The object of giving radiotherapy in this group, however, is to relieve symptoms. Its effect should, therefore be judged by the relief given and not by the survival time which, though usually reported and occasionally of interest, is really irrelevant in these patients

Most patients with inoperable bronchial carcinoma who are suffering no great discomfort are best not treated by radiotherapy at all, since the course of treatment merely keeps them attending or living in a hospital during the last period of their lives which they might enjoy at home with their families There are obvious exceptions, for instance the nervous person who is aware of the diagnosis and particularly anxious to have something done In these patients treatment—particularly if of short duration and given as an out-patient—may be of value and can be repeated later if necessary The use of antibiotics alone may lead to great improvement in patients with collapse and infection, and has certainly made irradiation much easier and safer. In general the art of radiotherapy in this group lies in selecting the patients most likely to benefit and in obtaining that benefit as quickly and easily for the patient as possible (Smithers 1955). If a patient is old and feeble with a short expectation of life, relief of symptoms may often be obtained by simpler and less enervating forms of treatment If he is young and fit, a prolonged course of irradiation, even for symptomatic relief alone, may be justified, especially if it can be shown that this particular symptom is unlikely to return again, if at all, until shortly before death

It is important for radiotherapists, who see so many of these patients, to consider the much neglected palliative value of resection As Bignall showed (1955), the mode of dying when the affected lung has been removed is less liable to be by a prolonged and painful illness The value of palliative resection (Abbey Smith 1957) is discussed in Chapter XXI. It is not only in the less advanced cases that consultation between thoracic surgeon and radiotherapist before treatment may be of benefit to the patient.

Relief of Symptoms

The symptoms which may be relieved by radiotherapy are cough, pain, haemoptysis, dyspnoea, dysphagia and superior mediastinal obstruction (Churchill-Davidson 1955).

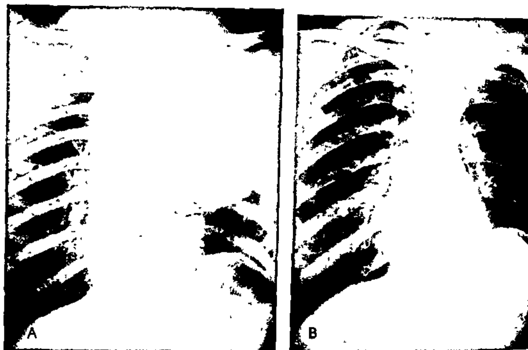


Fig 54

Female, aged 30, with undifferentiated carcinoma treated by x-rays in November 1938. Radiographs before (A), and 1 year after treatment (B) Patient lived for 4½ years following irradiation

Satisfying relief from cough is obtained in less than half the patients treated, haemoptysis in at least two-thirds; dyspnoea is partly but usefully relieved in rather more than half and dysphagia in rather less. Each individual must be judged separately according to general condition, education, desire for something to be done, histological tumour type, degree of spread, expectation of life and response to treatment. A nervous person with haemoptysis is usually worth treating, since relief can often be obtained within a week; a patient with troublesome dyspnoea who has had a large tumour mass (Fig 54), or who has suffered collapse of lung or lobe, especially if he has an undifferentiated tumour (Fig 55), may also get rapid relief with tumour regression or re-expansion. Dysphagia due to lymph node pressure may require fairly high dose, localized treatment over a period of three to four weeks for worthwhile palliation, and such treatment is usually unjustified in the very ill patient.

Relief of pain requires special consideration because of its particular difficulty in bronchial carcinoma. It is probable that much disappointment with radiotherapy has occurred because of a failure to distinguish between the different types (visceral, mediastinal, invasive and metastatic) in which the value of irradiation varies greatly (Blanshard 1955) Visceral pain often responds at first but is infrequently relieved completely or for long, and the

position with mediastinal pain is rather worse Pain derived from direct invasion of the pleura and chest wall is more amenable, and treatment well worth trying, even though this pain, too, may be most refractory at times The pain of brachial plexus involvement is, however, peculiarly disappointing for palliation by radiotherapy. Localized pain from individual metastases in bone is regularly relieved

Superior vena caval obstruction is the single most important indication for palliative irradiation in bronchial carcinoma (Fig 56). It is effective in the great majority of cases, and if a tumour dose of not less than 3,000r in three weeks is given, the condition seldom recurs before death, even if it does it is usually less severe, coming on more slowly and allowing further time for a collateral circulation to be established.

Pleural effusion was for long regarded as a contra-indication to palliative irradiation, on the grounds that a rapid increase in fluid might occur While these patients usually do badly, there is no reason to withhold irradiation which is designed to relieve some other symptom solely because of the effusion The treatment of malignant pleural effusions themselves is discussed later under radioactive isotopes.

The combinations of symptoms, personality, family, and doctors concerned are many, and the problems presented usually difficult Thoughtful care of

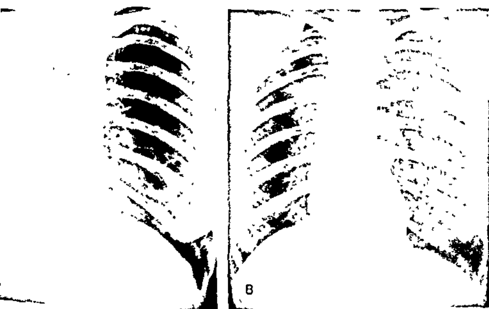


FIG 55
Female aged 49, (A) before irradiation, and (B) 5 weeks after treatment, showing re-expansion of the right lung

the patient and some attention to the worries of his relatives rather than enthusiasm for one particular treatment method are needed. Radiotherapy, when used for inoperable patients, is only part of the general care and management of those approaching death. What is said may be more important than what is done, the number of visits made than the number of treatments given, the judgment of the moment to use chlorpromazine, cortisone, physeptone or heroin than the number of roentgens prescribed.



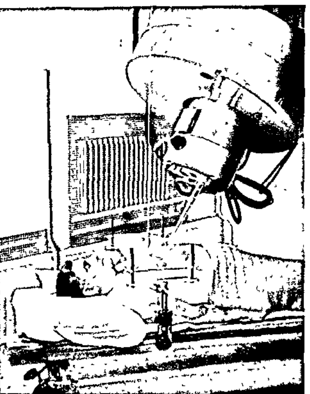
Fig. 56

Male, aged 61, (A) *before*, and (B) *after, x-ray treatment for relief of superior vena caval obstruction.* This patient died 15 months after treatment without any return of signs of mediastinal compression.

Supervoltage Treatment

Wheatley, Steed, Savage, King, Forster, Hodt, Jones and Smithers (1955) mentioned the first 25 patients with inoperable disease treated at the Royal Marsden Hospital with the two million volt apparatus (Fig. 57). Hare and Trump (1954) also gave an account of 25 similar cases and Guttmann (1955) reported 100 patients also treated at 2 MeV, in 10 of whom resection had previously been attempted but tumour left behind, the remainder being inoperable; in this group 27 lived one year or more, 11 had reached 2 years, with 4 surviving longer, 1 for more than four years. Watson (1956) reported 27 patients treated on the betatron at 23 MeV, and Morrison and Deeley (1957) [illegible]

relief of symptoms is being attempted, this may well be so when large field, low dose treatment is used. In our experience supervoltage *irradiation* gives symptomatic relief more easily and with far less discomfort to the patient. Improved quality of radiation also gives a better chance to those few patients whose degree of spread has been over-estimated or who are technically inoperable but in whom some *opportunity for longer survival* still remains



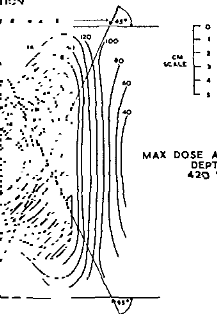


FIG 57

Two million volt short axis rotation treatment for a patient with a bronchial carcinoma

the patient and some attention to the worries of his relatives rather than enthusiasm for one particular treatment method are needed. Radiotherapy, when used for inoperable patients, is only part of the general care and management of those approaching death. What is said may be more important than what is done, the number of visits made than the number of treatments given, the judgment of the moment to use chlorpromazine, cortisone, physeptone or heroin than the number of roentgens prescribed.



FIG 56

Male, aged 61, (A) before, and (B) after, x-ray treatment for relief of superior vena caval obstruction This patient died 15 months after treatment without any return of signs of mediastinal compression

Supervoltage Treatment

Wheatley, Steed, Savage, King, Forster, Hodt, Jones and Smithers (1955) mentioned the first 25 patients with inoperable disease treated at the Royal Marsden Hospital with the two million volt apparatus (Fig. 57). Hare and Trump (1954) also gave an account of 25 similar cases and Guttmann (1955) reported 100 patients also treated at 2 MeV, in 10 of whom resection had previously been attempted but tumour left behind, the remainder being inoperable; in this group 27 lived one year or more, 11 had reached 2 years, with 4 surviving longer, 1 for more than four years. Watson (1956) reported 27 patients treated on the betatron at 23 MeV, and Morrison and Deeley (1957) 199 patients treated on the 8 MeV linear accelerator and observed for one year. Garland and Sisson (1956) suggested that palliation in inoperable cases was no better with supervoltage than with 250 kV x-rays. Since nothing more than relief of symptoms is being attempted, this may well be so when large field, low dose treatment is used. In our experience supervoltage irradiation gives symptomatic relief more easily and with far less discomfort to the patient. Improved quality of radiation also gives a better chance to those few patients whose degree of spread has been over-estimated or who are technically inoperable but in whom some opportunity for longer survival still remains

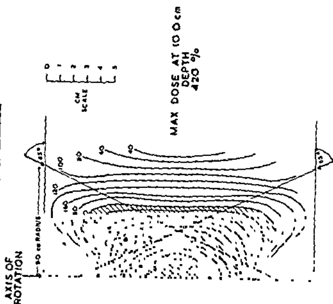


Fig. 57

Two million volt short axis rotation treatment for a patient with a bronchial carcinoma

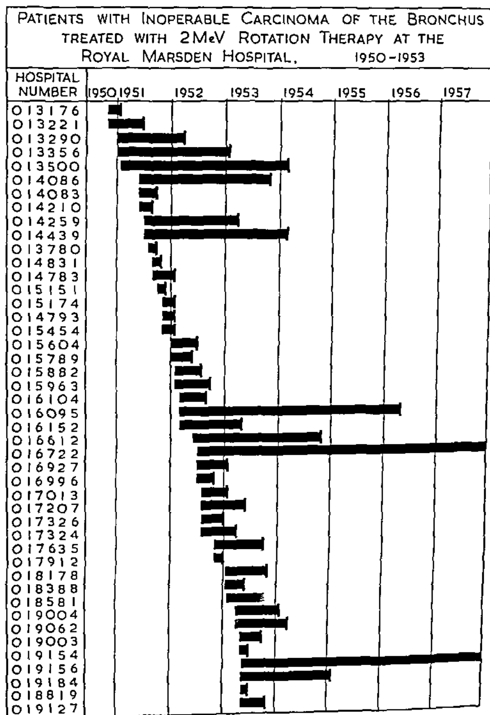

PATIENTS WITH INOPERABLE CARCINOMA OF THE BRONCHUS TREATED WITH 2MeV ROTATION THERAPY AT THE ROYAL MARSDEN HOSPITAL, 1950-1953
HOSPITAL NUMBER
1950
1951
1952
1953
1954
1955
1956
1957
013176
013221
013290
013356
013500
014086
014083
014210
014259
014439
013780
014831
014783
015151
015174
014793
015454
015604
015789
015882
015963
016104
016095
016152
016612
016722
016927
016996
017013
017207
017326
017324
017635
017912
018178
018388
018581
019004
019062
019003
019154
019156
019184
018819
019127

FIG 58

(Fig 58) A few patients with apical tumours involving the upper ribs have been treated by us at 30 MeV to test the palliative value of supervoltage irradiation in this most difficult group. Such treatment has also been reported by Haas, Harvey and Melchor (1957). Bone pain was relieved more easily than that due to nerve involvement, and good regeneration of eroded ribs obtained at times (Fig 59). Relief was too often temporary to be of any great value in the small number so far treated in this way but the method has not yet had a fair trial.

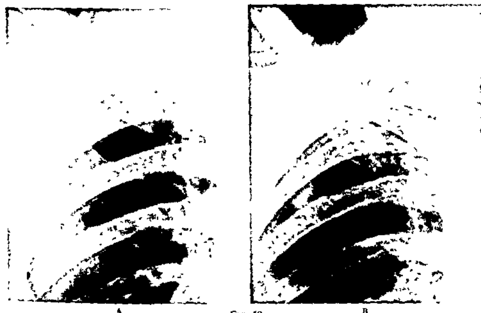


Fig 59

Male, aged 49, (A) before treatment, and (B) after treatment, on the 30 MeV synchrotron showing tumour regression and regeneration of third right rib

Radioactive Isotopes

The bronchoscopic implantation of radon seeds has been practised by Ormerod for many years (1937) and an account of his late results was given in 1953. One hundred patients were treated, 22 survived more than one year, 4 survived for 5 years, and 3 were still alive at 10 years Fermont (1944) reported another patient treated in this way in 1937 who was alive, well and working seven years later Despite the theoretical disadvantage of attempting a satisfactory tumour implant via the bronchoscope, there is no doubt that useful palliation is obtained with this method at times and that an occasional long survival resulted in the 1933 to 1939 period when criteria of operability were far narrower than they are to-day. These results, however, are yet another indication of the possibility of long-term bronchial carcinoma regression following irradiation.

Bronchoscopic tumour infiltration with colloidal gold (^{198}Au) has also been performed (Becker, Werner, Kuttig, Scheer and Weitzel 1957). A cannula is inserted into the tumour at bronchoscopy and the radioactive gold injected in several places.

The introduction of radioactive colloids directly into the bronchial tree was tried by Meneely, Auerbach, Woodcock, Kory and Hahn (1951) with the idea that their absorption would produce subsequent irradiation of the lymphatics draining the tumour-bearing lung. It was found that colloidal particles were slow to reach the mediastinal, bronchial and tracheal nodes, taking some two weeks for adequate localization. Since ^{198}Au colloid was used with a half-life of 2·7 days, the radioactivity had declined too far before the material reached its destination. Hahn and his co-workers experimented with silver colloids and with gold colloids silver-coated and gained much more effective localization in the lymph nodes of animals (Hahn 1956). Work on dogs has also been done by Bryant, Berg and Chrisophersen (1953) and by Wheeler, Jaques, Allen, Soltes, O'Connor and Black (1956). The difficulties involved in the development of this technique for the treatment of patients are considerable, not least of which is overcoming the block produced in the lymphatics leading to those nodes which it is most desired to reach and the flow by collateral lymphatic drainage leading away from the involved nodes which follows this obstruction. Clinical work with radioactive silver-coated gold colloids employed in addition to pneumonectomy offers some theoretical interest and its results will be worthy of further study.

Muller and Rossier (1951) introduced radioactive particles in suspension directly into branches of the pulmonary artery using ^{198}Au and ^{65}Zn. Powdered charcoal particles of average size 30–50 μ in diameter have also been used, with gold precipitated on their surface. The gold is made radioactive in a reactor after precipitation. These particles, in a pectin-containing solution with the addition of some of the patient's own heparinized blood, have been injected into branches of the pulmonary artery supplying the affected lobe by means of a cardiac catheter. This work has been repeated by Pochin, Cook, Cunningham, Hollman, Hudswell and Payne (1954). There is no doubt of the effective localization of radioactivity by this method, but little experience as yet of what may be achieved with it.

Muller (1951) and Walton and Sinclair (1952) introduced the use of radioactive fluids in the pleural cavity for palliation in malignant pleural effusions. Rapid accumulation of fluid after tapping with the need for repeated aspiration may be arrested at times by the use of radioactive colloidal gold ([illegible] 1957) or nitrogen mustard (Weisberger, Levine and Storaasli 1955; [illegible] When [illegible] wo days [illegible] t or two [illegible] al shift. when the gold is to be inserted because of distress due to [illegible] If the gold is diluted by too much fluid the dose rate is greatly reduced. After the gold (usually 80–100 mc) has been instilled, the patient is nursed in a 'tipping bed' and counting over the pleural cavity is performed to see that a

uniform distribution has been obtained In only one of our cases has the radioactive fluid loculated; 50 per cent of the gold was recovered by needling and no high dose effect observed. From 1949 to 1956, 103 patients with malignant pleural effusions were treated by us in this way; 19 had primary bronchial carcinomas There was no effect in 4 of these 19 patients but in 4 the treatment was completely successful in that no further tapping was required; two of these patients lived for more than one year. The other results were intermediate, the treatment being of definite value in about half the cases treated

The Royal Marsden Hospital and Brompton Hospital Series

In 1944 the two hospitals set up a joint consultation clinic for the study and treatment of patients with bronchial carcinoma Its first report was published in 1951 (Brooks, Davidson, Price Thomas, Robson and Smithers) From May 1944 to December 1950 it formed a reference clinic mostly for inoperable patients for consideration of radiotherapy From 1951 onwards it was also given the task of recording and studying every patient with bronchial carcinoma attending the two hospitals as described in Section Four

This report on the radiotherapy of bronchial carcinoma carried out at the two hospitals covers three periods Some account of the first two has already been given by Davidson, Smithers and Tubbs (1951) and of the third by Bignall (1955)

The first period was from January 1938 to April 1944 and was concerned with all patients with this disease seen in the Radiotherapy Department of the Royal Cancer Hospital, later renamed the Royal Marsden Hospital, the second was from May 1944 to December 1950 and included all the patients with bronchial carcinoma seen either at the Joint Consultation Clinic or at the Royal Marsden Hospital, the third period was from 1951 to 1955 inclusive and included every new patient seen at both hospitals with this diagnosis The first period contains nothing more than a few patients seen in the radiotherapy department before any liaison with a chest hospital was established, the second a larger group of inoperable cases, mostly referred for radiotherapy after this association had started, and the third the total experience of this disease over five years in two hospitals, one devoted to chest disease and one to malignant disease in general, observed from one to five years later. It was only during the third period that a proper group of less advanced operable cases was included in the survey or that supervoltage irradiation became available

Radiotherapy Department Cases 1938–44

These were few, being only 134 patients in six years—an average of 22 per year—of whom 19 (14 per cent) lived one year or more (Table LVII) Some useful palliation was obtained, but the problem of bronchial carcinoma was not a major one in an otherwise busy department, and chief interest centred on the two patients who lived for more than five years One of these, treated in 1939 when aged 65, died almost exactly 7 years later, away from our observation,

TABLE LVII

Survival Among All New Patients with Carcinoma of the Bronchus Seen in the Radiotherapy Department of the Royal Cancer Hospital January 1938 to May 1944

Year	Number of patients seen	Number alive at the end of								
		1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	14 years
1938	22	5	1	1	1	0	0	0	0	0
1939	28	2	1	1	1	1	1	1	0	0
1940	19	2	1	1	1	1	1	1	1	1
1941	14	2	0	0	0	0	0	0	0	0
1942	24	2	2	1	0	0	0	0	0	0
1943	20	3	0	0	0	0	0	0	0	0
1944	7	3	2	0	0	0	0	0	0	0
Total	134	19	7	4	3	2	2	2	1	1

his death certificate stating that the cause was metastases from carcinoma of the lung. The second, with a squamous-cell carcinoma, was treated in 1940 when he was 58 and lived to be a great trouble to his three daughters and to die at the age of 72.

Joint Consultation Clinic and Royal Marsden Hospital Cases 1944–50

This was the period in which experience of the use of radiotherapy in palliation for patients with bronchial carcinoma was built up in the clinic by the treatment of much larger numbers. Eight hundred and eleven patients were seen in 7 years—an average of 116 a year—of whom 128 (16 per cent) lived for one year or more. There is no doubt that many patients derived no benefit from the treatment and that our tendency at first was to treat hopefully without due regard to what might be achieved. Certainly too many had a prolonged, so called 'radical', course of treatment when something simpler would have done as well. A very considerable burden of suffering was, however, relieved in a group of people for whom little had been done before. While there was no doubt of its value, the very fact of treating so many patients without any chance of success in terms of long survival in the vast majority, raised a number of internal problems. To keep the staff from becoming either careless or callous over this particular work, special investigations were started to add interest. The site, age, sex, histological type, length of history, delay in treatment, and frequency of symptoms first noticed by the patient or first taking him to his doctor were analysed (Bjork 1947; Brooks, Davidson, Price Thomas, Robson and Smithers 1951), the duration before seeking medical advice and the delay thereafter before treatment were noted, residence from birth, occupation from leaving school and smoking habits were recorded, responses assessed according to histology and situation of primary tumour, chemotherapy trials initiated (Boyland, Clegg, Koller, Rhoden and Warwick

1948), rotation therapy techniques adopted (Smithers 1955), and post-mortem studies of the distribution of metastases made (Galluzzi and Payne 1955, 1956) The problem of the care of large numbers of patients with incurable disease and the decision of when to give irradiation, how much and for how long for the best relief of symptoms with the minimum of added discomfort still remains.

A few patients during this period survived a long time Each one of these was subjected to a detailed review of the evidence on which the diagnosis had been based—clinical, radiological and histological. Wherever there was reasonable doubt of the diagnosis it was rejected and the patients shown in Table LVIII remain Some few operable cases were included in this period,

TABLE LVIII

Survival Among All New Patients with Carcinoma of the Bronchus Seen in the Joint Consultation Clinic and at the Royal Marsden Hospital May 1944 to December 1950

Year	Number of patients seen	Number alive at the end of											
		1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years	11 years	12 years
1944	79	9	2	1	1	1	1	1	1	1	1	1	1
1945	121	21	5	2	1	1	1	1	1	1	1	0	0
1946	132	17	5	3	3	1	1	1	1	0	0	0	0
1947	120	22	14	8	6	3	3	3	3	3	0	0	0
1948	107	19	6	4	2	2	2	2	2	0	0	0	0
1949	120	17	4	3	2	1	1	1	0	0	0	0	0
1950	132	23	6	5	4	3	2	0	0	0	0	0	0
Total	811	128	42	26	19	12	11	9	8	5	2	1	1

Treatment given to those surviving for 5 years and more
4 had radiotherapy + surgery and survived for 9, 9, 7 and 7 years
2 had surgery only and survived for 9 and 10 years
6 had radiotherapy only and survived for 12, 9, 8, 8, 7 and 5 years

since all patients referred to the Royal Marsden Hospital were considered and not only those attending the Radiotherapy Department

The grounds for the rejection of the diagnosis in those who had already been treated for this disease are of interest: in 6 the diagnosis was in doubt, some palliative treatment was given, and the patients all died soon after without certain confirmation of the origin of their malignant disease, in 9 the diagnosis was in doubt and some palliative treatment or a test dose to gauge radiosensitivity was given and a diagnosis of some non-malignant condition was soon established; in 5 the diagnosis of metastases in the chest from primary tumours elsewhere was established or strongly suspected These 20 patients were given small doses and none of them were seriously irradiated for a suspected primary bronchial carcinoma in an attempt to eradicate the disease In 11 other patients, however, the position was rather different (Table LIX) All had a serious attempt at treatment on the grounds that a primary bronchial

TABLE LIX

Patients Treated for Bronchial Carcinoma by Radiotherapy in whom the Diagnosis was Subsequently Rejected

Case number	Year	Patient's sex, age and hospital number	Clinical evidence	Bronchoscopy	Pathological evidence	Treatment	Survival	Final diagnosis
1	1944	Male, 38 (21/44)	Haemoptysis	Ulceration seen	Undifferentiated carcinoma*	5,500r in 36 days	Alive and well 13 years	Inflammatory carinal ulceration
2	1945	Male, 61 (001316)	X-ray	None	None	5,500r in 30 days	Alive and well 5 years†	Not made
3	1946	Male, 68 (004092)	X-ray	Normal	Undifferentiated carcinoma*	5,600r in 28 days	No recurrence, alive and well 5 years†	Suppurative pneumonia
4	1946	Male, 65 (003732)	Haemoptysis, X-ray	Narrowing and rigidity	Sputum twice positive for carcinoma*	4,300r in 33 days	Died 4 years	Coronary thrombosis, chronic bronchitis
5	1946	Male, 59 (003141)	X-ray	Normal	Sputum suspicious of squamous-cell carcinoma	4,200r in 29 days	Alive and well 6 years†	Bronchiectasis
6	1947	Female, 50 (005393)	X-ray	Normal	Squamous-cell carcinoma in supraclav. node*	3,300r in 29 days	Alive and well 9 years	Not made
7	1947	Male, 36 (006022)	Haemoptysis X-ray	Normal	Sputum suspicious of carcinoma	5,500r in 40 days	Alive and well 8 years	Inflammatory middle lobe lesion
8	1949	Female, 55 (009515)	Pain, cough	Distortion of carina, narrowing, node involvement	None	6,600r in 44 days	Died 1 year	Pulmonary tuberculosis
9	1949	Female, 58 (010986)	Cough, swelling of fingers	Tumour seen	Squamous-cell carcinoma*	6,100r in 36 days Lobectomy	Died 2 years, bronchopleural fistula	Fibroma
10	1950	Male, 66 (012864)	Haemoptysis, X-ray	Tumour seen	None	5,400r in 40 days	Killed by lorry 2 years	Not made (Coroner's post-mortem)
11	1950	Male, 62 (013174)	X-ray	Narrowing	None	5,500r in 40 days	Alive and well 3 years†	Non-malignant bronchial stenosis

* Withdrawn on review of slides. † Discharged from follow-up.

Note The original diagnosis of carcinoma bronchus was rejected in the case of one patient (male, 58 (003213)), but was confirmed 8 years later when he died with multiple metastases

carcinoma was present. All were seen by a chest physician, thoracic surgeon and radiotherapist, and were accepted for treatment on what seemed adequate grounds. All have had the diagnosis rejected on review. Five of these patients had had a positive histological report, 3 on pieces removed for biopsy at bronchoscopy, one on a lymph node removed from the neck, and one on two specimens of sputum. One positive biopsy report proved, on review, to have been a clerical error in typing for another patient, three positive reports were withdrawn on review of the sections on the grounds that the specimen had really been inadequate for a satisfactory examination in the first place. Two other patients had had doubtful evidence for carcinoma based on sputum examination only. One patient was killed by a lorry two years after treatment, the pathologist who performed the autopsy for the coroner stated that he had not found any evidence of a lung tumour and, since there had been some doubt about the cause of his upper lobe collapse although a tumour had been seen, the diagnosis was withdrawn. In four or five of these cases some uncertainty still remains as to whether it was right to withdraw the diagnosis, but the evidence has been regarded as quite insufficient to include them as radiotherapy successes. One patient, however, in whom we rejected the diagnosis because of doubt had to be reinstated because he developed multiple bone metastases 8 years after his x-ray therapy.

Brompton Hospital and Royal Marsden Hospital Cases 1951–55

In this period 1,749 patients were seen and an average of 350 patients with bronchial carcinoma were registered each year, of whom 527 (31 per cent) lived one year or more. The Joint Consultation Clinic continued to function as before, but a few changes were made. Supervoltage x-ray treatment (2 MeV) and ^{198}Au colloids for instillation became available in 1950, and radioactive gold grains for implant were first used for bronchial tumours in 1955. A 30 MeV synchrotron was available for treatment for a short while and some patients with bronchial carcinomas (mostly superior sulcus tumours) were

TABLE LX

New Patients with Carcinoma of the Bronchus First Seen at the Royal Marsden Hospital and the Brompton Hospital from 1951 to 1955

Year	Number of patients seen	Number treated	Treatment method			Not treated
			Surgery only	Radiotherapy only	Surgery and radiotherapy*	
1951	343	192	53	129	10	151
1952	334	173	65	97	11	161
1953	383	210	72	122	16	173
1954	342	193	71	110	12	149
1955	347	203	78	117	8	144
Total	1 749	971	339	575	57	778

* Includes 8 patients treated by radiotherapy before resection.

treated with it. Interest was expanded to include a review of the results of treatment by all methods and a movement made towards their integration An account of this period is given in Section Four.

Table LX records the distribution by treatment method of 1,749 patients first seen from 1951–55, and Table LXI gives the percentage survival after different periods of time, up to the end of 1956

TABLE LXI

The Survival Rates of All Patients Seen at the Royal Marsden and Brompton Hospitals from 1951 *to* 1955 *from the Date of their First Attendance at these Hospitals*

	At risk	*Died in period*	*Untraced*	*Alive at end of period*	*Survival rate (per cent)*
1 year	*1,749*	*1,194*	*28*	*527*	*30*
2 years	*1,402*	*1,175*	*16*	*211*	*16*
3 years	1,060	946	8	106	10
4 years	677	623	3	51	8
5 years	*343*	*322*	*1*	20	*6*

13 patients treated by radiotherapy lived for more than 3 years and 5 for more than 4 years. All 20 patients living for 5 years were treated surgically.

DISCUSSION

[illegible] has been chiefly given by x-rays and [illegible] In relief of symptoms [illegible] *superior mediastinal* compression, haemoptysis, and painful metastases. Some patients have survived long periods following such treatment, a few of whom were inoperable because of tumour situation only. *Evidence provided by these cases and also* from pre-operative irradiation, post-mortem studies and a recent experiment in the treatment of operable cases, suggests that there may be a place for external beam therapy in attempts at cure. No real trial of supervoltage irradiation in selected operable cases has yet been made. With surgery hoping to extend treatment to more patients in the pre-symptomatic phase, a proportion of operable cases—particularly in the less favourable undifferentiated group—*may now receive a proper supervoltage* treatment trial.

Several new radioactive isotope *treatment methods are being tried but* most of them offer little prospect of success The implantation at thoracotomy of ^{198}Au grains, or of ^{192}Ir sources does seem, however, to be a worthwhile advance for patients with tumours which are *found to be too extensive* for resection

Progress in radiotherapy for patients with carcinoma of the bronchus depends on co-operation between surgeons and radiotherapists both before and *during treatment*, and also on a joint review of the results *obtained in all* patients seen, however they were treated.

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treated with it. Interest was expanded to include a review of the results of treatment by all methods and a movement made towards their integration An account of this period is given in Section Four.

Table LX records the distribution by treatment method of 1,749 patients first seen from 1951–55, and Table LXI gives the percentage survival after different periods of time, up to the end of 1956.

TABLE LXI

The Survival Rates of All Patients Seen at the Royal Marsden and Brompton Hospitals from 1951 to 1955 from the Date of their First Attendance at these Hospitals

	At risk	*Died in period*	*Untraced*	*Alive at end of period*	*Survival rate (per cent)*
1 year	1,749	1,194	28	527	30
2 years	1,402	1,175	16	211	16
3 years	1,060	946	8	106	10
4 years	677	623	3	51	8
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CHEMOTHERAPY

D. A. G. GALTON and ROSE PAPAC

NITROGEN MUSTARDS

THE first clinical trials of the nitrogen mustards were performed during World War II under conditions of secrecy and the results were not published until the war was over (Gilman and Philips 1946; Goodman, Wintrobe, Damashek, Goodman, Gilman and McLennan 1946; Wilkinson and Fletcher 1947). These early results indicated that the nitrogen mustards were effective in relieving symptoms and in causing regression of tumour masses in cases of Hodgkin's disease, lymphosarcoma, the chronic leukaemias, polycythaemia vera, mycosis fungoides and occasionally in malignant neoplasms with extensive metastases Treatment was confined to patients in the terminal stages of their disease, who were judged to be unsuitable for other forms of therapy. Improvement in cases of advanced carcinoma of the bronchus was early reported (Rhoads 1946; Boyland, Clegg, Koller, Rhoden and Warwick 1948)

As experience accumulated, nitrogen mustard and its allies were recognized to be of therapeutic value in Hodgkin's disease, the lymphomas and chronic leukaemias and their use is now routine. By contrast, their role in the routine management of carcinoma of the bronchus is still not clear although numerous reports have appeared and many hundreds of patients must have been treated The beneficial effects described are genuine enough but the likelihood of producing them is unpredictable; they are mostly transient and of limited clinical significance, with the exception of the syndrome of superior vena caval obstruction in which striking relief has been reported to follow treatment with nitrogen mustard.

Primary carcinoma of the bronchus was at first thought to respond better than other carcinomas to nitrogen mustard therapy, and one explanation put forward was that a higher concentration of drug reached the growth following intravenous injection. However, the regression of distant metastases could not be accounted for in this way, and it was pointed out that bronchial carcinomas derive much of their blood supply from the bronchial arteries (Wood and Miller 1938) Furthermore, subsequent experience has shown that nitrogen mustard and its allies sometimes have an effect in other neoplasms, particularly carcinomas arising from breast, ovary, testis, salivary glands, and less often in neuroblastoma, chorionepithelioma and other rare tumours (*Symposium on Alkylating Agents*, New York, 1957).

In this article we review the relevant literature in an attempt to define the place of chemotherapy in the routine treatment of bronchial carcinoma, and we discuss methods for conducting clinical trials with new agents.

Clinical Effects

Boyland, Clegg, Koller, Rhoden and Warwick (1948) reported 40 patients treated intravenously with di-2-chloroethylmethylamine (HN_2). Single doses of 0·2 to 0·4 mg. per kg. of body weight were given and injections were repeated once or several times in 14 cases. Twenty-four patients were stated to have obtained relief from their most distressing symptoms and in 18 cases objective evidence of benefit was recorded. Eight of 35 cases showed radiographic improvement, pleural effusions were resorbed in 5 of 13, improvement in neurological signs occurred in 1 of 10, and objective changes in metastases were recorded in 4 of 10 cases. Symptoms of superior vena caval obstruction were relieved in 3 of 5 patients and when pain was a major symptom it was relieved in 8 to 48 hours. The duration of benefit in this series was from 2 to 12 weeks. Nothing comparable was reported in a group of 22 patients treated with other drugs including urethane, oestrogens and an amino-stilbene. The surviving patients of this series and a further 20 patients similarly treated were subsequently observed by the group of clinicians at the Joint Consultation Clinic of the Brompton and Royal Marsden Hospitals. In their opinion any benefit conferred was slight and outweighed by the side effects associated with nitrogen mustard therapy (Brooks, Davidson, Price Thomas, Robson and Smithers 1951).

Subsequent studies have added little concerning therapeutic effects. Ben-Asher (1949) noted relief of superior vena caval obstruction for 3 months following 4 injections of 0·1 mg. per kg of body weight in a case of anaplastic carcinoma. One patient with squamous carcinoma secured relief of chest pain, cough and haemoptysis for 6 weeks, but 9 other patients obtained no benefit; in 6 of these the growth was squamous-celled and in 3 anaplastic.

Even in the most favourable reports, the apparent remissions rarely exceeded 6 months, and the majority were less than 3 months Once the patient had relapsed it was rarely possible to obtain a second remission with nitrogen mustard, although this has been recorded (Craver 1949; Kent and Reh 1950; Lynch, Ware and Gaensler 1950) The side effects of nitrogen mustard therapy cannot be ignored. Many patients experience nausea and vomiting which are not always abolished by giving the drug on an empty stomach after premedication with chlorpromazine and barbiturates. Furthermore, nitrogen mustard is a powerful depressant of haemopoietic tissue and it is therefore essential to perform blood counts at intervals of not less than two weeks during and for six weeks after each course of treatment. The simultaneous administration of corticosteroids and nitrogen mustard has been reported to lessen the side reactions; but the therapeutic effects were no better than those obtained with nitrogen mustard alone (Jones 1957). Weisberger, Heinle and Levine (1952) suggested that simultaneous administration of 1-cysteine could diminish the severity of leucopenia induced by nitrogen mustard, but later work suggested that the protection of 1-cysteine was not predictable enough to be of value (Levine and Weisberger 1955). Hatch, Bradford and Ochsner (1956) treated with radiotherapy 20 patients who had already received nitrogen mustard, and

felt that the response was better than in patients treated with x-rays alone. Lochman and Morris (1956), however, could not confirm this.

Superior Vena Caval Obstruction

There have been several reports of relief of superior vena caval obstruction. Roswit and Kaplan (1949) stated that they preferred nitrogen mustard to radiotherapy in this condition because they thought the response was quicker and there was no risk of exacerbating the symptoms by causing oedema, which they believed could occur with x-rays. Later, however, Roswit, Kaplan and Jacobson (1953) considered radiotherapy to be the treatment of choice. Radiation oedema had not occurred in 28 patients and radiation sickness was rare. Twenty-one patients treated by radiotherapy obtained remission of obstruction lasting 6 to 12 months in 6 cases, 1 to 6 months in 10, and less than 1 month in 5, whereas no patient treated with nitrogen mustard obtained relief lasting more than 5 months, 8 were improved for 1 to 5 months, 4 less than 1 month, and 3 did not respond. The authors therefore relegated nitrogen mustard therapy to a secondary role, useful when radiotherapy was no longer practicable or effective. Karnofsky (1956) advocated both nitrogen mustard and radiotherapy in the treatment of superior vena caval obstruction. Symptoms were thought to be relieved more rapidly by nitrogen mustard, there was no danger of oedema, and after a course of nitrogen mustard it appeared to be safe to give radiotherapy more rapidly than usual.

Relief of Toxic Symptoms

Apart from the relief of superior vena caval obstruction, the most dramatic clinical benefit claimed for nitrogen mustard therapy is the relief of toxic symptoms. Decrease in sputum production, improvement in well-being and gain in weight are reported to have occurred in over half of the patients in the series of Boyland and his colleagues (1948). In addition, subsidence of sweats and pyrexia are recorded by Roswit and Kaplan (1951) and in most reports decrease in haemoptysis is also noted (Ben-Asher 1949; Kent and Reh 1950). This relief of the signs and symptoms of persistent sepsis could be accounted for either by a bacteriostatic action of the nitrogen mustard or by shrinkage, however slight, of the bronchial growth, thus permitting drainage. In the following case the relief of sepsis was striking and the rapid and sustained improvement in pain associated with hypertrophic pulmonary osteoarthropathy suggests that the beneficial effects of treatment resulted from some action on the tumour itself. Had the drug acted only as a bacteriostatic, the arthropathy would probably not have been affected.

Mr G. B., aged 59 years, developed pain in his feet, hands, knees and elbows in February 1947. This was followed by fatigue, cough, chest pain and haemoptysis. The diagnosis of anaplastic columnar cell carcinoma was established by bronchoscopy. Thoracotomy in January 1948 revealed an inoperable neoplasm infiltrating the mediastinum and trachea. On examination in January 1948 he had advanced clubbing of fingers and toes and a small effusion of the right knee joint. HN_2 was given in doses of 0·2 mg./kg. in 4 injections at 2-week intervals,

After the first injection, pain in the wrists, ankles and knees improved rapidly haemoptysis ceased and he gained weight. Five months later his condition rapidly deteriorated with a return of joint pain, weight loss and increased chest pain; a mass appeared over the second right rib anteriorly. He died in August 1948, 7 months after the initiation of HN_2 treatment, 19 months after the onset of his disease.

In the following case, major toxic symptoms resulted from bronchial obstruction by an adenoma. Relief of toxic symptoms was obtained twice, first by injections of nitrogen mustard, and in the second instance by penicillin therapy.

Mrs L. P., aged 47, developed anorexia, weight loss, chest pain and chronic cough in 1944; a similar episode occurred in 1945. In 1946 haemoptysis began and subsequent bronchoscopic biopsy was reported to show adenocarcinoma. Her condition deteriorated and upon admission to the Royal Marsden Hospital in March 1947, under the care of Mr R. W. Raven, she was cyanosed. There was impairment of movement of the right hemithorax with a mediastinal shift to the right. Chest x-ray showed a homogeneous opacity obscuring the right lung field.

Owing to her poor general condition, radiotherapy was not given. She was treated with dimethylmonochloroethylamine, 5 mg./kg., intravenously. Subsequently she felt better, there was less dyspnoea and she gained 8 pounds weight in one month In June 1947 the chest x-ray showed some aeration of the right upper zone.

For a year her general condition was good: then the cough increased, mid-sternal pain developed and chills and night sweats began. A chest x-ray showed several fluid levels in cysts in the right lung Bronchoscopy was repeated in June 1948, a large nodular pinkish-yellow mass was seen in the right main bronchus just below the carina. Biopsy was reported to show bronchial adenoma.

A febrile illness occurred in July 1948, associated with the cough and chest pain. This subsided with penicillin therapy.

In January 1949 right pneumonectomy was performed by Sir Clement Price Thomas; the lung was extensively adherent and was replaced by multiple cysts. Histological examination confirmed the diagnosis of bronchial adenoma. The patient remains well.

In this case, improved bronchial drainage and relief of suppuration followed treatment both with a nitrogen mustard and later with an antibiotic. The progressive development of cysts in the lung suggested the operation of a check valve mechanism by the adenoma, which may have occluded the right main bronchus during expiration. Slight regression of the adenoma would then have relieved obstruction enough to permit drainage. Such regression might have resulted from a direct effect of the nitrogen mustard on the tumour or from subsidence of inflammatory changes associated with it.

Regression of Tumours

There is direct and indirect evidence that nitrogen mustard can cause tumour regression Skin and lymph node metastases have been observed to regress (Karnofsky 1956, personal observations), collapsed lobes have

re-expanded, while the occasional relief of hemiplegia and papilloedema have suggested direct effect on cerebral metastases (Levine and Weisberger 1955). The relief of superior vena caval obstruction must also result from diminution in size of the mediastinal tumour. In the following case diminution in the size of skin deposits and of the mediastinal shadow occurred and the relief of pain associated with skeletal metastases may well indicate a direct effect of the nitrogen mustard on the bone deposits.

Mrs A. M., aged 63 years, had a febrile attack in May 1947, followed by recurrent haemoptysis, progressive dyspnoea and loss of two stones in weight; in June 1947 she developed pain below her right knee and later dysphagia. On examination in November 1947 she was a thin pale woman with occasional explosive cough. Positive findings were a hard left axillary lymph node, a hard subcutaneous nodule 0·5 cm. in diameter above the left iliac crest and a tender diffuse spindle-shaped swelling over the upper fibula. Bronchoscopic biopsy was consistent with oat-cell carcinoma, biopsy of the skin nodule showed an alveolar adenocarcinoma whose morphology was compatible with bronchogenic origin. Chest x-ray showed a mass spreading out from the left hilum, x-ray of the right tibia and fibula showed metastasis of the head and neck of the right fibula.

She was treated initially with HN_2, 0·2 mg./kg. for 3 doses. After the first dose of HN_2 there was subjective improvement together with radiographic regression of the left hilar mass and diminution in size of the subcutaneous nodule.

Nine weeks after the final injection she noted dyspnoea, occasional haemoptysis and three new skin nodules. A second course of HN_2 was again followed by subjective improvement, weight gain, regression of skin deposits, and disappearance of haemoptysis. Ten weeks later she again relapsed with a mass appearing in the right loin and with enlargement of skin nodules. She was then treated with HN_3 (tris-chloroethylamine), a total dose of 0·1 mg./kg. in 5 injections. Appetite returned, dyspnoea and dysphagia were relieved, haemoptysis ceased and one skin nodule regressed slightly.

She died after a massive haemoptysis in June 1948, seven months after starting treatment, thirteen months from the initial symptoms of her disease.

Absorption of Malignant Effusions

Boyland, Clegg, Koller, Rhoden and Warwick (1948) observed resorption of pleural effusions in 5 of 13 cases following intravenous injection of nitrogen mustard; and similar results have been obtained by others (Roswit and Kaplan 1951; Levine and Weisberger 1955). Weisberger (1957) has reported favourably on the effect of direct intrapleural instillation of nitrogen mustard on malignant effusions. 0·4 to 0·6 mg. per kg. of body weight were injected into the pleural cavity after removing as much fluid as possible. In 5 of 9 cases of bronchial carcinoma the results were reported to be beneficial and to compare favourably with those obtained with radioactive gold. Weisberger states that intrapleural instillation of nitrogen mustard offers a unique opportunity of placing a drug directly in contact with neoplastic cells. Given by this route, nitrogen mustard caused less leucopenia than by intravenous administration. It is, of course, not always clear whether pleural effusions result from lymphatic obstruction alone, from infiltration of the pleura by malignant growth or from infection.

Histological Changes Induced by Nitrogen Mustard

The clinical evidence reported indicates that nitrogen mustard ha direct, if limited, effect on the growth of bronchial carcinoma. Opportunit for serial histological study of tumours during and after treatment have be few, while the pleomorphism characteristic of primary bronchogenic carcinom and the erratic tendency of malignant growths to undergo degenerative change and necrosis has made the interpretation of changes in serial specimen hazardous. Attempts to relate clinical benefit to histological type have led to conflicting opinions; but this is of little significance because the therapeutic results are so poor.

Craver (1949), Roswit and Kaplan (1951), and Roswit, Kaplan and Jacobson (1953) found that the best therapeutic results occurred in anaplastic growths. Roswit and his colleagues pointed out that 90 per cent of patients who developed superior vena caval obstruction had anaplastic growths and that in this syndrome nitrogen mustard therapy frequently gave worthwhile results. The two best results in Kent and Reh's series (1950) were in patients with undifferentiated growths, and Lynch, Ware and Gaensler (1950), Levine and Weisberger (1955), and Karnofsky (1956) also found that such growths responded better. On the other hand, Hatch, Bradford and Ochsner (1956) found no relation between clinical response and histological type in their 198 cases.

The histological changes in the growth following nitrogen mustard therapy are similar to those that have been reported to occur in normal tissues under experimental conditions Many of the observed effects result from interference with cell division. Cells prevented from dividing grow to enormous sizes, while incomplete divisions result in bizarre deformities of nuclear structure, such as multinucleate giant cells or cells with misshapen hypersegmented nuclei. More seriously damaged cells show unrecognizable masses of nuclear material amongst disorganized cytoplasmic masses. Gaensler, McKay, Ware and Lynch (1948) studies serial histological specimens in 8 cases. Although no changes were found that could not also be observed in untreated tumours, all the post-treatment specimens showed definite changes compared with pre-treatment material from the same patients. In their series of 60 patients, undifferentiated growths were generally associated with better clinical response to nitrogen mustard therapy, yet the most profound histological changes were seen in squamous and epidermoid carcinomas. Undifferentiated tumours showed mainly cell necrosis and reduction in frequency of mitoses, whereas epidermoid growths showed giant cell formation, nuclear and cytoplasmic disintegration, nuclear malformations, cellular giantism and abnormal mitoses.

The Place of Nitrogen Mustard in Routine Treatment

Since there is little evidence that nitrogen mustard therapy prolongs life, there is no indication for using it in every case of bronchial carcinoma. There would appear to be a limited scope for giving nitrogen mustard to relieve symptoms; but here again the small likelihood of bringing about worthwhile benefit, the short duration of improvement and the high incidence of nausea,

vomiting and leucopenia make it difficult to give precise indications for its use. Our ten years' experience with nitrogen mustard therapy at the Joint Consultation Clinic has made it impossible for us to be enthusiastic No one need feel negligent if he omits to give nitrogen mustard But if radiotherapy is not available or if there are contra-indications to its use, it would be reasonable to give a course of nitrogen mustard, and this is likely to be of most value in the presence of superior vena caval obstruction Our experience of its use in the treatment of this condition has been limited because at the Joint Consultation Clinic superior vena caval obstruction has been regarded as an indication for immediate radiotherapy.

Newer Chemotherapeutic Agents

Nitrogen mustard is one of a class of compounds known as alkylating agents. These are substances that under certain conditions can combine with electron-rich groups; phosphate groups particularly are present in biological materials in high concentration and alkylating agents have a strong affinity for them. Chlorambucil, melphalan, tri-ethylene melamine, tri-ethylene thiophosphoramide, chloroethylmethanesulphonate, mannitol mustard and dopan are newer alkylating agents that have undergone clinical trials (*Symposium on Alkylating Agents*, New York, 1957) None has proved to be superior to nitrogen mustard in the treatment of primary carcinoma of the bronchus

Clinical Assay of Therapeutic Agents

The approach of the clinician engaged in routine therapy conflicts with that required in the clinical evaluation of a new form of treatment The essence of the conflict is that in routine therapy the clinician is preoccupied with the welfare of his patients as individuals, and the means of achieving their welfare are of secondary importance When orthodox methods of treatment have been exhausted it is very convenient for the clinician to have at hand some ancillary method The patient and his family feel that something active is still being done for him and that his case is, after all, not hopeless There is a tendency for new methods of treatment to be used in this way and the nitrogen mustards have often been prescribed as placebos This practice cannot be too strongly condemned The essence of a placebo is that it should be harmless and pharmacologically inactive. If nitrogen mustards are given in full doses they are not harmless and if they are given in doses too small to be effective they are being wrongly used. The worst possible justification for the use of nitrogen mustards or other substances given in this way is the belief that when sufficient cases have been collected the results of treatment can be analysed, so permitting definitive statements to be made concerning the value of the treatment In practice, records of patients so treated are useless. Facts do not emerge unless the treatment given is part of an inquiry so planned that answers to specific questions are obtained, or is so effective as to change the whole outlook on the treatment of the disease The form of inquiry varies according to the nature of the disease under investigation In carcinoma of

the bronchus there are two necessary approaches. A new drug may be examined for its efficiency in relieving symptoms or in prolonging life. Small numbers of cases may yield valuable information concerning symptomatic relief but are unlikely to throw light on the effect of treatment on survival unless the new drug is of exceptional potency. Small differences in efficacy between two drugs can only be revealed by estimating the survival times in large numbers of cases.

In recording symptomatic relief or changes in physical signs or radiographs, subjective bias on the part of patient and doctor is very great. To avoid this, half of the patients may be treated with the drug under trial while the remainder receive the standard form of treatment. The cases are allotted on a random basis and the recording physician should be unaware which preparation is being administered to any particular patient. In practice this procedure is rarely possible because the drugs can often be identified by their side effects and most of them are so toxic that the physician must know their identity in order to take appropriate steps to regulate dosage. To overcome this, progress notes may be kept by an independent observer who is not directly concerned with the management of the patient. When assessing the results of treatment on symptoms and signs it is important that total clinical benefit be recorded. If beneficial changes in individual symptoms and signs in a series of cases are enumerated in isolation, it is quite possible to give the impression that a form of treatment has been effective when no single patient had derived total benefit in the sense that all the symptoms of which he was complaining had been completely relieved. It is essential to record also the duration of total benefit. An impressive list of symptoms stated to have been relieved by a particular form of therapy loses most of its point when further reading reveals that relief in many cases lasted only a week or two. It is also desirable to record all other treatments administered during the trial. It is useless to record the effects of a drug on pain if the quantities of standard analgesics given at the same time are not stated; similarly, precise details of antibiotics, steroids, blood transfusions, aspirations of serous effusions are required. These details are as important as are the facts on which the diagnosis is based, and clear statements on the reasons for including each patient in the trial.

The duration of untreated carcinoma of the bronchus is well known (Buchberg, Lubliner and Rubin 1950; Bignall 1955) as is the effect on survival of surgery in operable cases (Bignall and Moon 1955) and of radiotherapy in the inoperable (Bignall 1956) New material assembled in the same way and differing only in the addition of a new method of treatment should yield information on the effect of the additional therapy on survival. A major difficulty in planning such a trial is to decide the stage in the disease at which the new treatment is to be given. Hitherto, chemotherapy has usually been deferred until the disease was far advanced and the results have not yet been sufficiently encouraging to suggest that administration at an earlier stage might give better results. Nevertheless, by analogy with other diseases it is reasonable to suppose that in the event of an active agent becoming available, it would have to be used as early as possible to be fully effective.

Hitherto, the chemotherapeutic agents that have been tried in lung cancer have been cytotoxic substances, active against proliferating cells whether malignant or not. Perhaps too much emphasis has been placed on the necessity for eradicating malignant tissue. Bignall has pointed out (personal communication) that if tumour growth could merely be arrested and the associated metabolic disturbances counteracted, malignancy would lose much of its terror, even though the growth remained in the body Treatment with an anti-neoplastic agent that arrested tumour growth might have to be continued indefinitely, perhaps for the duration of the patient's life Such a substance would necessarily have properties very different from current agents; it would have to be free from toxic action on normal tissues and of troublesome side effects. Malignant growth is often regarded as differing from normal growth by lacking some controlling factor The recognition and identification of such a factor is a problem for the future; and for a long time to come we must expect chemotherapeutic agents to be developed along the present conventional lines; and progress will be in small steps

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APPENDIX I

SUPPLEMENTARY INFORMATION ABOUT MORTALITY FROM CANCER OF THE LUNGS

R. A. M. CASE

THE presentation of the statistical background to cancer (or any other) mortality to a diverse body of largely medical readers is a problem in itself. This Appendix is therefore devoted to a discussion of some aspects of vital statistics for the benefit of those who without it might find Section One a little obscure. The Appendix really consists of five more or less unconnected essays on background topics which are not essential to the development of the main theme of Section One (p. 11) but which must be understood in order to follow the argument. Some of the views expressed may be considered unorthodox, and for this reason are discussed in detail.

1. SOME OBSERVATIONS ON MORTALITY INDICES AND POPULATION ESTIMATES

Various simple arithmetical procedures can be applied to population and death data to produce a battery of mortality indices, but one index may be more appropriate than another in a particular set of circumstances.

Let us first consider what type of statement can be made by a mortality index. Broadly speaking, we may distinguish between what I shall call the *administrative* and what I shall call the *biological* statement. Either type of statement may be legitimate if it is appropriate to the question; either type may become illegitimate when inappropriate

As an example of the administrative question, let us consider the case of a maker of coffins who has just set up in business. He will wish to know how many coffins he may expect to have to make in a year, and the simple ratio:

$$\frac{\text{Number of deaths in England and Wales (D)}}{\text{Population of England and Wales (P)}} \times \text{Number of people in his area}$$

for the previous year may satisfy him. The first part of this ratio, $\frac{D}{P}$, is called the crude death rate. A comparison of a series of crude death rates for different dates should not, however, be used to answer the enquiry: 'Has the impact of killing disease on the community lessened in the last twenty years?', since although the crude death rate (male) *rose* from 12·9 per 1,000 for the decade 1921–30 to 13·0 in the next decade and fell to 12·5 in the decade 1941–50, a *considerable reduction* of the impact has in fact taken place. A consideration of the frequency with which death occurs at different ages will at once suggest an explanation of this paradox. Death is about ten times as frequent between the ages of 55 and 60 as it is between the ages of 20 and 25. For this reason an alteration in the age composition of the population alone may alter the crude death rate very considerably, although the impact of killing disease on the community may not have changed.

The most important step in refining a crude mortality index is the calculation of

age-specific death rates distinguished by sex. The estimated population and the deaths are put into similar age groupings and each death rate is calculated separately for each age group. Age-specific rates form the basis for most refined mortality indices.

It is desirable at this stage to consider what sort of statement is made by a mid-year estimate of population by age groups. In any age group a considerable proportion of its members will live throughout the calendar year, but deaths will occur throughout the whole year. Some members will die in the first half of the year, and others will live into the second half of the year, but die before the end of the calendar year. The number of deaths that occurs in the first six months of the calendar year is, for any age group in England and Wales at least, very nearly the same as the number that occurs in the second six months of the year. Without resorting to formal proof, we may take it that the mid-year estimate of the population for a particular age group can be accepted as a good estimate of the number of years of life lived in the calendar year in question by a group of people of the stated age passing through the whole year. This important proposition holds true to well within the limits of error in forming the estimate, although it could be disturbed by violent epidemics, catastrophes or mass migrations.

We can now see why the age-specific death rate is a measure of the intensity of the impact of a killing disease on a community of a stated age. If we visualize mortality as a threat of death, varying in intensity at different ages, that hangs over a population, we can measure the intensity of the threat at a particular age by allowing it to act on a number of individuals of the relevant age for a measured time and then counting the dead. This is strictly analogous to the situation referred to by an age-specific death rate. The rate is expressed as the number of deaths occurring per unit number (we shall most frequently use 1,000 in this Appendix and in Section One) of years of life lived by a group of persons whose ages lie between specified limits. By convention this is written as 'the age-specific death rate per 1,000 living per year'.

The procedure of forming age groups eliminates to a large extent the effect of the actual age of each individual by narrowing the age-range to a point where the variation of the actual ages becomes relatively unimportant. The members of the age group may differ in respect of many attributes, other than age, that render them more or less susceptible to the lethal force, but since we cannot measure these attributes we cannot take them into account in the calculations. It is, however, legitimate to construe the age-specific death rate as an estimate* of the average chance of dying within a specified unit of time (here one year) for all the individuals in the population under consideration whose ages lie within the limits prescribed by the age group. If it is conceded that it is legitimate to refer to the death rate as the *average* chance of all the members of the age group, it follows that it can also be used in the sense

*Formally, the measure of the chance of dying within one year after attaining the exact age x is the life table death rate, q_x, given approximately by the expression $\frac{D}{P + \frac{1}{2}D}$ where P refers to the mid-year estimate for the age group x to $x + 1$ years and D is all deaths in that age group during the year. In our discussion this difference between the two types of death rate is not relevant to the argument when we are referring to the mortality from all causes.

When dealing with the age-specific disease-specific death rate, however, the death rate for the age group x to $x + 1$ is obtained from the expression $\frac{d}{P}$ where d is the number of deaths from the disease under consideration, and the life table disease-specific death rate from $\frac{d}{P + \frac{1}{2}D}$. In our discussion, therefore, we can regard the age-specific disease-specific death rate as, in the sense given above, an estimate of the chance of dying from the disease under consideration within a stated time (here one year) *if no other fatal disease intervenes*.

that it is the *average* chance referable to each member of the age group, although the *specific* individual chance is incalculable because of the lack of information about attributes other than age.

Both the crude death rate (male and female) and the age-specific death rate may be further differentiated into disease-specific rates by using the number of deaths classified by disease instead of the total deaths from all causes; although as the number of deaths in each subdivision gets smaller the chance of sampling errors in the estimate will increase, and it may become necessary to combine the data into year groups, say quinquennial or decennial, as well as age groups. It is useful to have both the year and age groups of the same size.

Since the age-specific death rate from all causes is the sum of the disease-specific death rates for that age group, a change in one disease-specific death rate need not affect any other disease-specific death rate, but only the total of the rates (the death rate for all causes). There may sometimes be biological reasons due to synergism or repulsion between particular diseases which would cause a reciprocal alteration of disease-specific death rates, but there is no constraint due to the calculation of the rate that prevents their being independent.

2. The Concept of Cohort Analysis and its Place in Gaining an Understanding of a Contemporary Array of Death Rates

I have given a fairly complete account of cohort analysis of death rates as a narrative technique elsewhere (Case 1956) In what follows I propose to discuss how an understanding of this method of analysis can help us in understanding the meaning of a contemporary array of death rates

A contemporary array of death rates has been defined (p. 13) as the series of age-specific death rates relating to a given date, and an example of a series of such contemporary arrays is found in Tables I and II (p. 13 and 14), where the mortality data for cancer of the lungs in England and Wales is set out in a form suitable for cohort analysis.

When we consider the figures shown in Tables I and II and start at the top left-hand corner (age 0–4, date 1911–15) we have an age-specific death rate referable to a group of people born around 1911. (For exact details of how the group is derived see Case (1956).) It is obvious that the age-specific death rate for the survivors of this group when they are in the age group 5–9 is found not under the date 1911–15 but under the date 1916–20, and so on diagonally across each Table

If we now draw the contemporary age-specific array for the date 1951–55 in the conventional manner, we can understand that each column is the age-specific death rate of the survivors of a group whose antecedent age-specific death rates fall along a line running back into the past and are not represented by any of the columns of the conventional representation

This can be illustrated as follows from simplified data. Suppose that we start with this imaginary contemporary age-specific death rate array for 1951–55:—

Age (years)	*Death rate per 1,000 living per year*
30–	17 0
40–	21 5
50–	30 2
60–	40 0
70–79	31 7

In terms of the conventional representation of age-specific death rates this would appear as in Figure 60. Each black panel represents the 1951–55 age-specific death rate for the appropriate age group. There is a tendency for the eye to run along the black panels and imagine that they form a series in the sense that one is the antecedent of the next as we progress up the age scale.

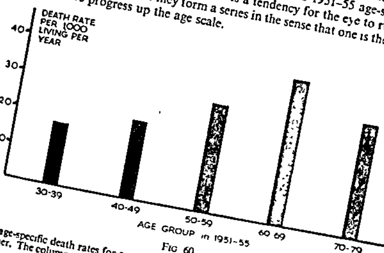


Fig 60

The age-specific death rates for a given date (here 1951–55) presented in the conventional manner. The columns are spaced more widely apart than is usual (From imaginary data.)

If we now consult Figure 61, where the black panels are identical with those of the conventional representation, we see that each black panel is in fact the latest of a series of panels (shown chequered) which represent the mortality of the particular 'cohort' at different dates (and hence at different ages) in time past A cohort is a group of people born during a specified period, and is referred to by the central date of that period; *e.g.*, the 1918-19 cohort were the people born around 1918-19.

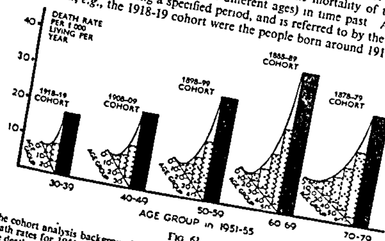


Fig 61

[Th]e cohort analysis background to the conventional representation of the age-specific [de]ath rates for 1951–55. The black panels are identical with those of Figure 60, and [th]e death rate scale refers only to these 1951–55 rates. The chequered panels represent death rates in ten-year age groups of the survivors of cohorts born around the dates shown (From imaginary data)

This representation makes it plain that no black panel can ever be in sequential series with any other black panel, and that the shape of the series suggested by the black panels may be very different from the shape of any of the series of antecedent chequered panels.

When we are dealing with any disease the mortality rate of which is to any extent influenced by nurture (and this includes a large proportion of all diseases) the difference between the series of chequered panels leading up to the contemporary black panel and the series suggested by the black panels alone may become very marked. Since only the chequered panels (which are often perforce unrepresented) are relevant to the way in which the rate represented by the black panel has evolved, a good knowledge of the social and medical history of the past is clearly necessary before attempting to interpret a contemporary mortality pattern.

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3. A Note on Age-standardized Summarizing Indices

A summarizing index is a single figure which emphasizes one particular aspect of a situation which has been described in statistical terms, and before deciding to employ such an index it is essential to have a clear understanding of the nature of the statement made by the index to be used. A survey of the current fashions of usage of summarizing indices, far from giving a clear impression of the issues which should be considered before undertaking such an analysis, might in fact suggest that some one procedure is able to bring all the relevant features of a situation into perspective.

This generalization is particularly relevant to a class of indices widely used in the study of mortality rates and known as age-standardized summarizing indices. They may take the form of numbers, rates or ratios and the ones which are relevant to our subject are the 'expected' number of deaths; the age-standardized death rate; and the age-standardized mortality ratio.

Numbers

One of two concepts, that of the 'expected' number of deaths and that of its corollary, the 'observed' number of deaths, is common to all these indices.

The 'Expected' Number of Deaths can be defined as the number of deaths that would be expected to occur in a defined population in a stated time if certain specified conditions were fulfilled. In order that this number may be calculated it is necessary to have:—

(i) A statement of the age-specific death rates that are assumed to be operating.

and (ii) A definition of the population which includes a statement of the number of years of life lived by its members in the age groups to which the age-specific death rates refer (As we have already seen (p 271) the mid-year estimates of population in age groups give this information for each calendar year of the stated period.) The population 'defined' in this way may be an actual or an hypothetical one.

(The worked Example (pp. 276–277) of calculating summarizing indices shows such information in columns 1–6.)

The 'expected' number of deaths is arrived at by the addition of the results of multiplying each age-specific death rate by the number of years of life lived by the population of that age group in the stated period. (See columns 9, 10, 12 and 13 of Example.)

The 'Observed' Number of Deaths is simply the total number of deaths that did in fact occur in an actual defined population in a stated time. Clearly our knowledge of this number is not dependent on prior knowledge of the age-structure of the population or of the age-specific death rates that actually obtained. (See columns 2 and 5 of Example.) It is also clear that if the population used above for the calculation of an 'expected' number of deaths is an actual and not an hypothetical population it will give rise also to an 'observed' number of deaths.

Rates

By dividing by the total number of years of life lived by the defined population in the stated period of time, both the 'expected' and the 'observed' number of deaths may be converted into a rate, which can be expressed in any convenient unit, e g, death rate per 1,000 living per year

Crude Death Rate

From what has been said on page 270, we can see that the 'observed' number of deaths, when expressed in this way, gives the crude death rate of the population. (See columns 2 and 5 of Example)

Age-standardized Death Rate

The rate produced by the division of the 'expected' number by the defined population is known as the age-standardized death rate (See columns 9, 10, 12 and 13 of Example.) The statement made by this rate can now be seen to be 'This is what the crude death rate for the population would have been if some other specified set of age-specific death rates had been operating', and falls, with the crude death rate, into what has previously (p 270) been called the 'administrative' class of statement.

The defined population, if it is an actual population, can obviously give rise to only one 'observed' number of deaths and to only one crude death rate. Any defined population, however, whether real or hypothetical, can be used as a base for the calculation of an unlimited series of 'expected' numbers and age-standardized death rates, by the use of different sets of age-specific mortality rates.

Ratios

For purposes of comparison, the numbers and rates described may be expressed as ratios, for example:—

$$\frac{\text{Expected number}}{\text{Observed number}} \left(\text{or } \frac{\text{Age-standardized Death Rate}}{\text{Crude Death Rate}}\right) \text{ for a defined population}$$

or, in the case of two 'expected' numbers derived from two sets of age-specific death rates (X and Y) acting on one defined population —

$$\frac{\text{Expected number from X}}{\text{Expected number from Y}} \left(\text{or } \frac{\text{Age-standardized Death Rate from X}}{\text{Age-standardized Death Rate from Y}}\right).$$

These may be left as simple ratios or, as in the *Standardized Mortality Ratio*, may be expressed as a percentage, when equality is indicated by 100

Each of these ratios, derived as they are from 'observed' and/or 'expected' numbers of deaths in a defined population, describes the interaction of one defined population with each of two sets of age-specific death rates. The value of such a ratio will clearly depend on the age distribution of the chosen population; the effect of the age-specific death rate corresponding to a large age group in the population will be emphasized, whereas a small age group will diminish the effect of the corresponding age-specific death rate. This type of summarizing index provides, therefore, no absolute comparison between two sets of rates and, for any two given sets of age-specific death rates, the ratio obtained may well vary according to the base population chosen.

The ratio type of summarizing index will remain constant, whatever the base population, in only one set of circumstances: that the mortality pattern for a particular disease is irrevocably determined at birth and for any population this pattern is accurately reflected in the contemporary array of age-specific death rates, even though the intensity of the lethal force may vary from population to population. If a changing environment or a changing genetic inheritance plays any part in determining the mortality pattern, the contemporary array of age-specific mortality rates will not show an unchanging shape, as we have learned from cohort analysis (p. 272).

The method of derivation of examples of these indices and a comparison of the statements made by them is shown in the Example (pp. 276–277). Two imaginary countries, A and B, are used in this analysis, and the mid-year populations are shown in columns 1 and 4. Country A has hitherto been an under-developed country. The population has not been healthy, famine has been rife and the care of the elderly, whose constitution has been undermined by these circumstances, has been poor. Recently, the country has been devastated by war and the population between the ages of 15 and 50 sadly depleted. As a consequence, the population figures taper off very rapidly with advancing age. Country B, on the other hand, has not suffered such disadvantages. Its climate is in general healthy, its food production adequate, its physicians skilled, its statesmen wise and its neighbours peaceful This has resulted in a low mortality amongst the elderly and a happy immunity from catastrophic depletion of the young adults. As a consequence, the numbers in the population taper off relatively slowly with advancing age

The deaths per year from an imaginary disease X are shown in columns 2 and 5. Disease X is one with a marked environmental element in its aetiology and has a long and variable latent period between the application of the environmental stimulus and the appearance of the disease In country A the environmental factors which cause the disease have been much in evidence only during the last 40 years. In country B they used to be widespread, but were to some extent controlled between 40 and 50 years ago and have been kept under control since then. As a consequence, those under 50 years of age in country A have a relatively high mortality, whilst those over 50 are less severely affected. The young men in country B never lived through times when the environmental influence was very marked and so have a relatively low mortality rate, whilst the older people, who have been exposed to the risk, show a high rate of mortality.

The differences between the age-structures of the populations of the two countries and the differences between the age-specific death rates from the disease X in the two countries, as we have just seen, have been caused by two different and largely unconnected sets of circumstances. In order to forestall a possible criticism that the hypothetical figures used show an extreme and unlikely difference, I quote the explicit view of the Registrar General (1940) as to the nature of a standardized death rate.

He writes: 'Standardized death-rates are attempts to express the mortality of a population of *changing* or *abnormal* age distribution by a single figure calculated in such a way that the changes or abnormalities in constitution do not appreciably affect it.' (Italics inserted.)

The question we are considering is how far any of the summarizing indices used can, in a *concise form*, give us useful information as to whether the lethal power of disease X is greater or less in country A than in country B, and by how much. The words '*concise form*' are used because an examination of the age-specific death rates (calculated from the numbers of deaths and the populations and shown in columns 3 and 6), which are prerequisites to the calculation of the summarizing indices already tells us that disease X shows a higher death rate in the young in country A than in country B, but that after the age of 50 the death rate is higher in country B. The measure of the difference at any particular age is, of course, found in the age-specific death rates themselves.

From the populations and age-specific death rates set out in the Example we can calculate three sets of indices:—

(1) *Standardization on Population A* is demonstrated in columns 8 and 9, which show the result of the operation of the age-specific death rates for countries A and B on a population whose structure is the same as that of country A.

(2) *Standardization on Population B*, where the two sets of age-specific death rates are assumed to be operating on a population of structure the same as the population of country B, is shown in columns 10 and 11.

(3) *Standardization on an Hypothetical Population*

Many types of hypothetical populations have been proposed for use in age-standardizing procedures. From 1901 to 1940 the Registrar General used a population known as the 'Standard Million', which had the 'age distribution of persons of undistinguished sex in the general population of England and Wales in 1901.' (Registrar General 1940.) Other authors have used the population of their own country in a particular year (e.g., Segi, Fujisaku and Kurihara 1957), or have attempted to form a synthetic population by adding together figures relating to a large number of countries (e.g., Segi 1957). Another form of composite hypothetical population was proposed by the Registrar General (1945) when he introduced the Comparative Mortality Index, a special form of standardized mortality ratio. This population was a population whose percentage age distribution was made up of the mean of the percentage age distributions of the two populations which had generated the two series of age-specific death rates that it was desired to compare.

In the worked Example (columns 12 and 13) the chosen hypothetical population is made up of the sum of the numbers in each age group of the populations of countries A and B. This type of hypothetical population is essentially that proposed by Segi (1957).

The standardized death rate and the standardized mortality ratio have been calculated in all these cases and are shown in the Example.

An examination of the results obtained (Terminal Statements, Example) will show that the summarizing indices calculated are not unanimous in deciding whether or not the lethal force of disease X is greater or less in country A than in country B.

Each of these ratios, derived as they are from 'observed' and/or 'expected' numbers of deaths in a defined population, describes the interaction of one defined population with each of two sets of age-specific death rates. The value of such a ratio will clearly depend on the age distribution of the chosen population; the effect of the age-specific death rate corresponding to a large age group in the population will be emphasized, whereas a small age group will diminish the effect of the corresponding age-specific death rate. This type of summarizing index provides, therefore, no absolute comparison between two sets of rates and, for any two given sets of age-specific death rates, the ratio obtained may well vary according to the base population chosen.

The ratio type of summarizing index will remain constant, whatever the base population, in only one set of circumstances: that the mortality pattern for a particular disease is irrevocably determined at birth and for any population this pattern is accurately reflected in the contemporary array of age-specific death rates, even though the intensity of the lethal force may vary from population to population. If a changing environment or a changing genetic inheritance plays any part in determining the mortality pattern, the contemporary array of age-specific mortality rates will not show an unchanging shape, as we have learned from cohort analysis (p. 272).

The method of derivation of examples of these indices and a comparison of the statements made by them is shown in the Example (pp. 276–277). Two imaginary countries, A and B, are used in this analysis, and the mid-year populations are shown in columns 1 and 4. Country A has hitherto been an under-developed country. The population has not been healthy, famine has been rife and the care of the elderly, whose constitution has been undermined by these circumstances, has been poor. Recently, the country has been devastated by war and the population between the ages of 15 and 50 sadly depleted. As a consequence, the population figures taper off very rapidly with advancing age. Country B, on the other hand, has not suffered such disadvantages Its climate is in general healthy, its food production adequate, its physicians skilled, its statesmen wise and its neighbours peaceful This has resulted in a low mortality amongst the elderly and a happy immunity from catastrophic depletion of the young adults. As a consequence, the numbers in the population taper off relatively slowly with advancing age.

The deaths per year from an imaginary disease X are shown in columns 2 and 5. Disease X is one with a marked environmental element in its aetiology and has a long and variable latent period between the application of the environmental stimulus and the appearance of the disease. In country A the environmental factors which cause the disease have been much in evidence only during the last 40 years. In country B they used to be widespread, but were to some extent controlled between 40 and 50 years ago and have been kept under control since then. As a consequence, those under 50 years of age in country A have a relatively high mortality, whilst those over 50 are less severely affected. The young men in country B never lived through times when the environmental influence was very marked and so have a relatively low mortality rate, whilst the older people, who have been exposed to the risk, show a high rate of mortality.

The differences between the age-structures of the populations of the two countries and the differences between the age-specific death rates from the disease X in the two countries, as we have just seen, have been caused by two different and largely unconnected sets of circumstances. In order to forestall a possible criticism that the hypothetical figures used show an extreme and unlikely difference, I quote the explicit view of the Registrar General (1940) as to the nature of a standardized death rate.

variations of the mortality within a country (e g., Registrar General 1957, see p. 33), when it is often the case that the sub-population under consideration is too small for the actual age-specific death rates to be calculated.

each hypothetical situation are known. Examination of the age-specific death rates themselves will, therefore, answer the question whether they are or are not the same,

reader is thereby deprived of the benefit of the information that was inherent in the age-specific death rates which were necessarily calculated in order to obtain the indices

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4. THE CONDITIONS UNDER WHICH A 'PARADOXICAL FALL' IN DEATH RATE WILL OCCUR IN A CONTEMPORARY ARRAY OF AGE-SPECIFIC DEATH RATES

The phenomenon of a fall in death rates in a contemporary array of age-specific death rates at a point where the relevant cohort death rates continue to rise will, in what follows, be called a 'paradoxical fall' It will always occur when a certain critical relationship between the cohort age-effect on death rates and the secular change of death rates is reached.

The Critical Relationship of Secular Change of Death Rates and Age-effect on Cohort Death Rates

We may now use part of the information given by Figure 2 of Chapter II (p 19) to see when this critical relationship will be reached The relevant section of this Figure has been redrawn in simplified form as Figure 62.

Let us consider the paradoxical fall of death rate that occurs in the 1946–50 contemporary array of death rates for cancer of the lungs in males The rates are

the diagram), but if we pass to the 70–74 age group of the cohort data (point C) we

As was anticipated, the result varies according to the base population used and none of the summarizing indices provides an absolute comparison between the two sets of age-specific death rates.

In short, age-standardized summarizing indices may not be able to help in answering *biological* questions about disease X, but may contrive only to obscure th information far more precisely and usefully conveyed by the contemporary arrays c age-specific death rates themselves

The Use of Indices

Having considered the limitations of summarizing indices, it is now pertinent for us to inquire what useful information may legitimately be gained from them.

Take the case of an 'observed' number of deaths and an 'expected' number be- upon some hypothesis, both derived from the same defined real population. Th are two possibilities:—

The 'observed' and 'expected' numbers may be sufficiently different for it to b inferred that the 'observed' number could not have resulted from the operation of the set of age-specific death rates specified by the hypothesis.

or The 'observed' and 'expected' numbers may not differ sufficiently to justify such an inference.

In the latter case we must reserve judgment. Since it is possible for the same 'expected' number to result from the operation of two or more different sets of age-specific death rates (Example, columns 12 and 13), we must refrain, even though the 'observed' and 'expected' numbers are *exactly* the same, from inferring that the particular set of age-specific rates specified in the hypothesis have been operating.

In what circumstances may the information to be derived from such a situation prove useful? As we saw earlier, the 'observed' number may be known without prior knowledge of the age-specific death rates that have been operating If we have sufficient information to calculate such rates we can, by direct inspection of them and of the age-specific rates specified by any hypothesis we wish to test, obtain more information than we should have done by the use of a summarizing index. In circumstances where it is not possible to calculate the actual age-specific death rates operating, the use of a summarizing index may or may not prove useful.

Imagine, for example, that we are comparing the mortality from a given disease in two different countries, for only one of which we know the age-specific death rates. The discovery, in such a case, that the two sets of age-specific rates in operation could not be the same would not be surprising, nor would such information be of much benefit to us.

Suppose, however, that of the two populations under consideration one is a sub-section of the other and can be regarded, apart from the attribute or attributes which allow it to be defined as a sub-section, as representative of the main population. It may not be possible to calculate the age-specific death rates for the sub-section, but it is possible to infer, from a comparison of the 'observed' number of deaths and the 'expected' number derived from the age-specific death rates of the main population, whether or not those rates can be operating on the sub-section. In such circumstances the inference that the age-specific rates operating on the sub-section are not the same as those operating on the main population can be linked with the attribute or attributes which distinguish the sub-section from the main population and may prove of very great value. Examples of such a situation are to be found in the study of occupational diseases (*e.g.*, Registrar General 1938) and also of regional

cohort age-effect in passing to the next higher age group 70–74 (point B), and this change is measured by the vertical line BD′. Obviously, whenever the secular change AD exceeds the cohort age-effect BD′ the contemporary array must show a fall of death rate along the line AB. Since the cohort age-effect in the cohort which includes the point A is a continued rise in the cohort death rate beyond the point A, the fall of rate indicated by the slope AB is a paradoxical fall

When a paradoxical fall in a contemporary array of death rates takes place in an array which has previously shown a rising death rate, as occurs in Figure 2, a peak as at A will be produced.

The most recent age-specific contemporary array of death rates, for 1951–55, shows a peak at point E in the diagram, followed by a fall along the line EC. We cannot formally discuss whether this is a paradoxical fall or not, since the cohort rates beyond the point E will have to be computed from observations to be made in the future There is, however, at present no reason to believe that the fall will not prove to be paradoxical.

5 A Note on a 'Legitimate and Useful' Use of the Crude Death Rate

The crude death rate, as we have seen (p 270), is very sensitive to the age-structure of a population, and it is therefore unsuitable for comparing mortalities from populations in different countries, or in the same country at widely differing dates. It will be reasonable to infer that actual changes of mortality are reflected by a series of crude death rates, referring to dates in a very short space of time in one country, if the population age-structure shows little change between the beginning and end of that period.

It was legitimate to illustrate the seasonal variation of lung cancer mortality (p. 31) by the use of crude death rates, because an inspection of the annual population estimates gave assurance that the age-structure of the population had not changed much. It was useful to do so because the quarterly figures for deaths from cancer of the lungs were not given by age, and therefore no age-specific death rates could be computed.

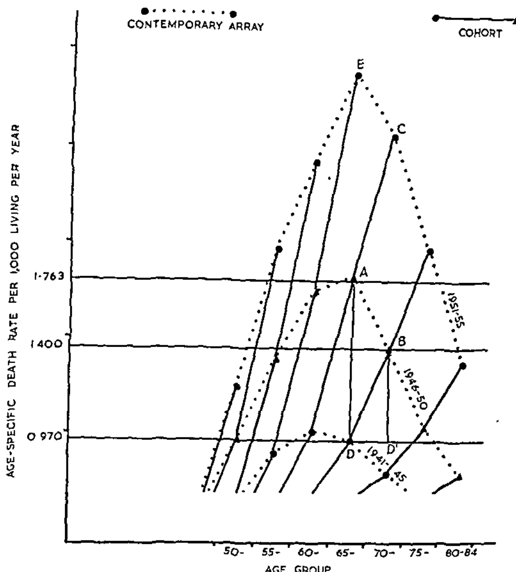


FIG 62

Detail from Figure 2 (Chapter II, p. 19).

The critical relationship between the secular change of death rates and the age-effect on cohort death rates necessary to produce a 'paradoxical fall' of death rate in a contemporary array of age-specific rates.

find that the cohort death rate has continued to rise. The explanation of this paradoxical fall in the contemporary array is to be found by considering the death rate of the 65–69 age group in 1941–45 (point D).

During the five-year interval between 1941–45 and 1946–50 two types of change of death rate referable to point D have taken place. One is the secular change in the death rate of the age group 65–69, measured by the vertical line AD. The other is the

TABLE LXII

Age and Sex of the Patients and the Histological Type of the Tumour

Histological type		*Age (years)*					*Age not known*	*Total*
		Under 40	*40–49*	*50–59*	*60–69*	*70 or more*		
Squamous	*M*	9	68	190	158	21	—	446
	F	—	2	18	17	2	—	39
	Total	9	70	208	175	23	—	485
Undifferentiated	*M*	10	65	185	137	17	1	415
	F	6	9	16	21	3	—	55
	Total	16	74	201	158	20	1	470
Adenocarcinoma	*M*	3	6	27	18	1	—	55
	F	1	2	6	5	—	—	14
	Total	4	8	33	23	1	—	69
Histological type known		29	152	442	356	44	1	1,024
Not known	*M*	14	74	212	229	106	1	636
	F	1	12	26	33	17	—	89
	Total	15	86	238	262	123	1	725
Total	*M*	36	213	614	542	145	2	1,552
	F	8	25	66	76	22	—	197
	Total	44	238	680	618	167	2	1,749

APPENDIX II

THE BROMPTON HOSPITAL AND ROYAL MARSDEN HOSPITAL SERIES

J. R. BIGNALL

THE following definitions have been adopted in order to simplify the analysis:—

Histological Type—Only three histological groups have been used: squamous, undifferentiated and adenocarcinoma. 'Oat-cell' and 'columnar cell' tumours have been included in the undifferentiated group, and 'alveolar cell' or 'bronchiolar cell' in the adenocarcinoma group. The sections have not been reviewed specially for this study. Each case has been placed in one of these groups on the evidence of the pathological report in the hospital notes, the type recorded in operation specimens and necropsy material being given preference to that from biopsy material when both were available. If many more sections had been examined from the whole tumour in each case, each one could probably have been more accurately placed in a histological category; if each section had been examined by many pathologists, variations of interpretation between the cases might have been reduced. However, although no doubt some of the tumours were, in fact, incorrectly classified, the information available on the histological type in the hospital records seems sufficiently accurate for rough comparisons within the series.

First Symptom—Many patients begin the illness with more than one symptom. To define the 'first' symptom is, therefore, not always possible. In transcribing the clinical records, an arbitrary classification of symptom patterns was adopted, giving precedence to the more dramatic and easily remembered complaints. The common symptoms were placed in the following order: haemoptysis, fever, chest pain, cough. Thus, if a patient was recorded as having begun the illness with haemoptysis and chest pain, the first symptom was recorded as 'haemoptysis'; a febrile illness with pleural pain was taken to be 'fever'; and cough was only considered to be the first manifestation of ill health if it appeared to have been a clear change in the quality or degree of a cough already present, or an entirely new symptom, and if there were none of the other three recorded. Dyspnoea, malaise and loss of weight were not recorded separately, but were grouped together as 'other symptoms'.

Duration of Symptoms before Diagnosis—A few patients had already been treated elsewhere before coming to the Brompton or Royal Marsden Hospital. Some had been investigated elsewhere and were referred for treatment or for further advice on the diagnosis. But the great majority were sent to the hospitals by general practitioners, either as the first step in hospital investigation or as the result of a report on a miniature x-ray. The recorded duration of illness before attendance is not, therefore, in all cases the same as the 'duration before diagnosis'.

Metastases at time of Diagnosis—As far as possible the record of the presence and location of metastases was made from the reports in the hospital notes of the first examination. It includes, therefore, only those metastases clinically or radiographically apparent and recorded. It does not include general wasting from probable but cryptic metastases

TABLE LXIV

The Duration to Examination Related to the Age and Sex of the Patients, Histological Type of Tumour and the First Symptom Recorded

	Duration from first symptom to examination (months)							Total
	0	1–2	3–5	6–11	12 or more	No symptom	Not known	
Sex *Men*	138	488	356	252	141	62	115	1,552
Women	16	51	49	45	11	4	21	197
Age (years)								
Under 40	3	13	12	7	4	—	5	44
40–49	23	94	43	33	19	14	12	238
50–59	*57*	*215*	*166*	*113*	*54*	*30*	*45*	*680*
60–69	51	180	144	113	58	20	52	618
70 or more	20	37	40	30	17	2	21	167
Not known	—	—	—	1	—	—	1	2
Histological type								
Squamous	44	142	104	89	45	23	38	485
Undifferentiated	40	157	112	70	47	20	24	470
Adenocarcinoma	5	14	19	16	5	6	4	69
Not known	65	226	170	122	55	17	70	725
First symptom								
Pain	37	123	76	50	23	—	6	315
Haemoptysis	49	65	41	30	27	—	5	218
Fever	27	108	71	54	33	—	5	302
Cough	16	124	120	96	47	—	13	418
Metastases	8	19	10	5	—		1	43
Other	17	99	86	59	21	—	61	355
No symptoms	—	—	—	—	—	66	—	66
Not known	—	1	3	3	1	—	21	32
Total	154	539	405	297	152	66	136	1,749

TABLE LXIII

The First Recorded Symptom Related to the Sex and Age of the Patients and the Histological Type of Tumour

	First recorded symptom								Total
	Pain	*Haem.*	*Fever*	*Cough*	*Metastases*	*Other*	*Nil*	*Not known*	
Sex *Men*	289	199	267	372	35	305	62	23	1,552
Women	26	19	35	46	8	50	4	9	197
Age (years)									
Under 40	8	4	13	10	1	6	—	2	44
40–49	49	30	44	48	7	41	14	5	238
50–59	121	70	130	169	14	137	30	9	680
60–69	110	86	106	139	12	132	20	13	618
70 or more	27	28	9	52	9	38	2	2	167
Not known	—	—	—	—	—	1	—	1	2
Histological type									
Squamous	75	77	104	110	4	84	23	8	485
Undifferentiated	86	57	90	113	19	80	20	5	470
Adenocarcinoma	15	6	10	13	1	18	6	—	69
Not known	139	78	98	182	19	173	17	19	725
Total	315	218	302	418	43	355	66	32	1,749

TABLE LXVIII

Treatment Related to the Age and Sex of the Patients, the Histological Type of the Tumour and the duration of Symptoms

	Thoracotomy							
	Total	*No resection*	*Resection*			*Radiotherapy only*	*Neither resection nor radiotherapy*	*Total*
			Pneum	*Lob*	*Total*			
Sex *Male*	475	113	268	94	362	511	679	1 552
Female	37	3	24	10	34	63	100	197
Age (years)								
Under 40	18	8	6	4	10	20	14	44
40–49	86	14	56	16	72	95	71	238
50–59	243	49	153	41	194	229	257	680
60–69	159	45	75	39	114	187	317	618
70 or more	5	—	1	4	5	43	119	167
Not known	1	—	1	—	1	—	1	2
Histological type								
Squamous	228	30	159	39	198	131	156	485
Undifferentiated	201	49	109	43	152	160	158	470
Adenocarcinoma	43	3	19	21	40	14	15	69
Not known	40	34	5	1	6	269	450	725
Duration of symptoms (months)								
No symptoms	42	2	19	21	40	8	18	66
0	53	14	24	15	39	47	68	154
1–2	158	43	90	25	115	188	236	539
3–5	110	28	61	21	82	155	168	405
6–11	81	19	51	11	62	97	138	297
12 or more	52	9	34	9	43	44	65	152
Not known	16	1	13	2	15	35	86	136
Total	512	116	292	104	396	574	779	1,749

TABLE LXVII

The Recorded Site of the Tumour Related to the Age and Sex of the Patients, the Histological Type, the First Recorded Symptom and the Duration to Diagnosis

	Site										Total
	R.U. lobe	*L.U. lobe*	*R.L. lobe*	*L.L. lobe*	*R. main*	*L. main*	*R. mid*	*Lobe not known*		*Not known*	
								R.	*L.*		
Sex *Men*	338	324	194	160	117	109	36	134	123	17	1,552
Women	39	19	21	19	20	17	2	31	26	3	197
Age (years)											
Under 40	4	11	4	2	7	1	5	2	8	—	44
40–49	54	36	28	28	17	16	6	32	16	5	238
50–59	157	132	96	58	59	52	14	61	48	3	680
60–69	131	124	74	76	41	50	10	49	52	11	618
70 or more	31	39	13	15	12	7	3	21	25	1	167
Not known	—	1	—	—	1	—	—	—	—	—	2
Histological type											
Squamous	116	84	88	57	55	42	10	12	19	2	485
Undifferentiated	97	88	71	55	47	38	19	29	24	2	470
Adenocarcinoma	11	26	9	7	1	5	1	3	5	1	69
Not known	153	145	47	60	34	41	8	121	101	15	725
First symptom											
Pain	72	78	32	29	17	20	6	29	30	2	315
Haemoptysis	52	31	34	30	20	16	5	11	16	3	218
Fever	58	46	54	43	36	25	4	19	15	2	302
Cough	86	83	45	40	34	31	12	48	38	1	418
Metastases	6	3	1	1	—	5	4	10	11	2	43
Other	78	86	33	23	26	25	6	40	31	7	355
Nil	19	11	12	11	—	2	1	4	5	1	66
Not known	6	5	4	2	4	2	—	4	3	2	32
Duration to diagnosis (months)											
0	35	24	21	17	16	8	4	9	16	4	154
1–2	114	119	63	50	31	38	12	65	45	2	539
3–5	88	83	51	32	32	34	9	38	36	2	405
6–11	60	49	33	41	30	27	5	26	23	2	297
12+	32	32	23	16	15	10	4	11	8	1	152
Not known	29	25	12	12	13	7	3	12	16	6	136
Total	377	343	215	179	137	126	38	165	149	20	1,749

D

E

F

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H